SUPPLEMENT

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Section I.—Medicine.

(*Continued.*)

DISCUSSION ON RENAL INEFFICIENCY.

Professor J. B. Cleland said the great advances had been made during the last few years in their knowledge of renal insufficiency. Various ingenious bio-chemical tests had supplemented the knowledge gained by clinical examination and by consideration of the more obvious changes in the urine. By an estimation of the blood urea they can anticipate or forestall the development of certain renal symptoms. The study of renal insufficiency was a common meeting ground for the physician, the surgeon, the physiologist, the bio-chemist and the pathologist. The comparative pathologist might be also associated with advantage.

The symptom complexes met with by the physician in renal insufficiency conformed to two main types which might be combined. He wanted to know from the bio-chemist how best to estimate the degree and the progress of the renal insufficiency and sought suggestions for treatment. He desired from the pathologist information as to the morbid anatomy changes that might be expected to be associated with various symptoms and he wanted to know if such changes invariably accompanied certain symptoms and whether lesions might be there but the symptoms absent or not yet manifested. From the morbid histologist he wished to ascertain the microscopical changes that could be detected and whether these might reasonably explain the clinical picture.

The surgeon had other but parallel problems. Renal insufficiency symptoms with him differed in some ways from those of the physician. He wanted to know when it was safe to remove an enlarged prostate and how an over-distended bladder should be relieved. He desired an explanation from the pathologist why, when certain over-filled bladders were relieved, polyuria developed and a form of uræmia resulted. He wanted an explanation of reflex anuria.

The physiologist could explain the functioning of the kidney as a whole and of its individual parts with the mechanics and physics of the process. In this connexion the recent view suggested that at any one time only certain sets of glomeruli and tubules were functioning, the others being at rest, might be of considerable moment.

The bio-chemist could gauge the functioning state of the organ.

It was the pathologist's difficult task to coordinate, if possible, the clinical and bio-chemical findings with the pathological changes present. Definite lesions might be present in the kidneys with a relative or complete absence of clinical symptoms, or there might be evident symptoms and definite bio-chemical changes with kidneys in which the lesions were relatively insignificant. The enormous reserve power of the kidneys might explain to some extent such apparent anomalies. Gross lesions might be present and yet one-fourth of functioning parenchyma might remain to stave off symptoms. Diffuse changes and less obvious damage to the sensitive cells might overstep the reserve without giving rise to obtrusive lesions. They wanted explanations from the pathologist of polyuria in chronic interstitial nephritis, of the changes associated with urea retention, of renal œdema.

Dr. C. H. Kellaway said that he proposed to confine his remarks to the question of renal function in nephritis. It was usually assumed that all the units of the kidney, the glomerulus and its tubules being regarded as a unit, were in activity at one and the same time and that failure of renal function occurred when a sufficient proportion of them were put out of action. Khanolkar, working in Boycott's laboratory, had shown, however, that a type of activity occurred in the kidney similar to that which had been shown to occur in the case of the voluntary muscles. The human kidneys contained about two million units and only a small proportion of these were normally active. Increased work meant that more units were thrown into activity probably by vasomotor influences.

This furnished an explanation of the fact that focal lesions in the kidneys did not necessarily imply obvious impairment of function. In conditions in which the lesions were widespread, as in nephritis, in bilateral infection and in cases with increased pressure in the pelvis of the kidney, there was generally impairment of function as judged by bio-chemical tests. This was so even when the damage was of patchy distribution.

A very large number of tests of renal function had been proposed in recent years and some had been found of great practical value. The type of functional impairment found appeared to depend on the point of incidence of the pathological change. If the damage was chiefly glomerular, there was failure in the excretion of water and salts. In patients thus affected œdema was prone to occur and they were benefited by a salt-free diet.

Leathes had showed that in normal persons the ingestion of water was followed by a copious diuresis and that in the morning a distinct alkaline tide occurred independently of alimentary events and as the result of increased activity of the respiratory centre in eliminating carbon dioxide after the period of sleep. In the presence of acute glomerular nephritis there might be no diuresis and no alkaline tide; if diuresis did occur in the less severe cases, it was unaccompanied by any increase in the total amount of sodium chloride excreted.

The test proposed by Linder, the administration of two grammes of potassium iodide at night and the collection of two consecutive twelve hour specimens of urine might also be of value in the estimation of glomerular function. In normal people nearly half the iodide was excreted in the first twelve hours. A word of caution was necessary

as it seemed likely that most cases of bromide and iodide idiosynerasy were due to renal insufficiency.

With reference to the reabsorbing function of the tubules Dr. Kellaway said that the most valuable tests were the determination of urea retention by the estimation of the blood urea and the urea concentration test proposed by Maclean. Professor Brailsford Robertson in his very interesting communication had attempted to remove some of the stumbling blocks in the way of correlation of the histological and functional findings in nephritis. There could be no question that the impairment of the permeability of the glomeruli led to the retention of salt and water. The retention of urea, "a no-threshold" substance, was generally attributed to a similar cause. This was unsatisfactory because urea retention occurred in a type of case in which not the glomeruli but the tubules were predominantly affected, and sometimes did not occur with general involvement of the glomeruli of extreme degree.

Robertson's suggested explanation of the retention of urea in cases of predominant tubular damage was that the permeability of the tubules was increased and that urea that passed through the glomeruli, was reabsorbed by the establishment of a "renal short circuit."

The main difficulty in explanation of the pathological functional changes in renal disease was the anomalous position of glucose. If it were possible to demonstrate that in normal individuals glucose was present in non-dialysable form and as such did not pass through the glomerular filter, this difficulty would vanish.

The value of the functional tests in prognosis depended on their repetition at short intervals and on the correlation of the results with the changes in the clinical findings. Single tests were of little value in determining the gravity of renal disease in any particular instance as acute mischief accompanied by gross functional derangement might clear away and leave little permanent damage in its wake.

Dr. Oliver Latham issued a warning against accepting as sufficient any one factor in the non-protein nitrogen, urea nitrogen, creatinin, uric acid and sugar content of the blood, for unless precipitation was complete, a false high non-protein nitrogen result could obtain. A low urea content was often associated with a high uric acid content in early interstitial nephritis and in gout and a high urea content improving with suitable dietetic treatment was of little value unless accompanied by a correlated creatinin diminution.

Again a high urea nitrogen reading might be associated with a temporary interference with kidney function such as would be brought about by shock, pain or other acute and temporary condition grafted on less severe chronic trouble and should not be interpreted as necessarily meaning a hopeless outlook.

cubic centimetres of blood nearly always meant a fatal cubic centimentres of blood nearly always meant a fatal outcome within two years. Four of his patients in whom the creatinin reading in the blood reached this figure, had died within twenty-four hours. Nevertheless on rare occasions a temporary high creatinin value in the blood might be observed accompanying acute disease and shock and the patient recovered. It was interesting to note from day to day the improvement in the clinical state and in the blood nitrogen content of patients who were being relieved. In conclusion Dr. Latham expressed the opinion that bio-chemical examinations of the blood which at the present time were expeditiously carried out, formed a useful guide to both physicians and surgeons in diagnosis and prognosis and in estimating the results of treatment.

FOCAL INFECTION.

By R. Scot Skirving, M.B.,
Sydney.

The matter for discussion which your secretaries have asked me to introduce to-day, is that of focal infection. It is a very wide subject and one which has closely and rightly engaged the attention of medical men in recent years. My few remarks do not pretend in any way to add anything to the knowledge of the matter, but merely to indicate how much debatable ground there is and what a far reaching influence on health such infection connotes not only concerning the local point of entrance of the mischief, but to what grave systematic troubles such local infections may lead. I shall, no doubt, omit as many instances of the connexion as I remember, but in the few sentences I am about to read, I shall easily bring to the minds of those about to speak the wideness of the influence of such infection, sometimes entering into the body in trivial or unobtrusive channels.

Let us first consider troubles affecting the mouth, the teeth, the nasal passages and the accessory sinuses. Whatever fashions in disease may dominate the medical mind at the present moment, dental sepsis, decayed teeth and pyorrhœa certainly occupy a prominent part. With the help of X-ray examination we are now usually able to discover with sureness septic lesions of or connected with the teeth and we know that by their timely removal a restoration to health is very often the happy result. It is indeed very difficult to avoid the conclusion that chronic dyspepsia and grave diseases, such as pernicious anæmia or ulceration of the stomach and duodenum, to name only two, are not the consequence of long neglected oral sepsis. It may be that at times our activity in the removal of doubtful teeth outruns our discretion or what is really justifiable from what we know of the connexion between focal infection and its supposed result. Still, allowing this, on the whole, the vigorous local treatment of pyorrhœa and septic stumps has produced beneficial results which the dental and medical profession may regard as a great advance. When I think of comparatively recent days, not only among the careless and ignorant, but among people who might have been expected to know better, in which there existed a foul necropolis of diseased teeth through the splintered remnants of which one dodged the spraying of sepsis as these patients spluttered their complaints on all about them, I realize that we really have advanced by attention to such matters., I am therefore satisfied that if by modern local treatment even a fraction of the evils attributed to such horrid conditions of the mouth is remedied, from local reasons alone we are doing well in cleaning up such dental sepsis which was clamant for cure.

I am equally convinced that neglected sinus trouble may also at times be productive of far reaching systemic infection. I call to mind two examples of sinus trouble, one of the frontal, the other of the antrum of Highmore, unrecognized, certainly untreated, where, in the one case an embolism of the central artery of the retina and in the other a slight hemiplegia, caused the temperature to be taken and a complete physical examination to be made,

with the result that ulcerative endocarditis was found to be present and of this distressful malady both patients died. Surely one was justified in attributing the infection to the foci I have named.

I have seen the same disease kill in which the focal lesion was a septic sore throat. In some such cases no antecedent lesion of the valves of the heart had existed; in others the more usual condition obtained that a prior damage to the valves was present. Such tragedies would almost certainly have been averted by timely local treatment.

The part the tonsil may play as the point of entrance to disease is now generally accepted. I recently was present at a meeting of specialists in diseases of children and of the throat. The discussion provoked my admiration because of the clarity and saneness of the views expressed. Tuberculosis, rheumatic affections and nephritis, to mention only three maladies, were mentioned as certainly or highly probably owing their origin to such a source. Functional albuminuria was another condition attributed to tonsillar sepsis. As to the latter I would certainly add my testimony that I have seen cases of this variety of albuminuria in which the removal of the tonsils was followed by the disappearance of the albuminuria.

In all the remarks made at that meeting I felt myself in full accord, with the exception of the statement that mere size of the tonsils was not an indication for their surgical diminution. Such a view to my way of thinking indicated a too great stress on the existence of sepsis in the tonsil as the only indication for removal. It is impossible for me to believe that two huge masses excluding the free entrance of air could do anything but harm, even if we allow that no sepsis was entering through that portal. I have seen, as all of us must have, poor, puny, dull half-asphyxiated children develope surprisingly, sleep well and become merry and intelligent after removal of large tonsillar masses which I think were not the seat of septic absorption.

Turning now to the middle and lower parts of the digestive tract we are perhaps as regards cause and effect on less sure ground. Yet I suppose here the relation between the two may be justly surmised. Take the number of cases in which the removal of the appendix has been followed by the disappearance of various functional troubles or perhaps organic changes in other parts of the digestive canal; surely such improvement is too frequent to be merely an accidental connexion, even if we admit some of the troubles recovered from were not due to septic absorption but to "reflex action," whatever view we hold of such nervous influence. I might here refer to that curious relationship which our fathers certainly believed in, *videlicet*, the occurrence of duodenal ulceration after an extensive burn of the body surface. While most of us have been content to suppose that it was due to septic absorption from the large denuded cutaneous surface, others have described the result as due to a trophic reflex disturbance, while others have declared that the connexion between the two was a purely accidental one. It certainly is a rare condition, but I must admit that I believe it is more than accidental; although in my life I have seen many great burns, I can only recall at most two occasions in which a proven or nearly certain duodenal ulcer followed a big burn.

The gall-bladder too plays a not unimportant rôle in the production of disease other than strictly biliary. The duodenum and the pancreas, as one would expect from their anatomical relationship with the common bile-duct, are the organs most usually involved secondarily to gall-bladder disease.

When I speak of the colon all things may be possible, although less surely certain than in most of the instances about which I have spoken.

The whole protean train of symptoms said to be due to auto-infection from a sluggish or altered colon indeed cover a wide area of human misery. General ill-health, altered temper, a muddy complexion, loss of sexual appetite or ability, to mention a few of the less lethal troubles attributed to malign absorption from the large bowel, are bad enough, but when we are sometimes forced to believe, by often quite excellent evidence, that anæmias of various degrees of deadliness may come from this source, it is evident that the intense therapy, general and surgical, which has been directed to abnormal states of the large bowel has no small justification. More difficult to accept in spite of the writings of several justly trusted observers is the causal connexion between colon-stasis and such widely different diseases as exophthalmic goitre and rheumatoid arthritis. I mention these two, but they do not nearly exhaust the list of troubles for which intestinal stasis and absorption is blamed. Of course we will all agree that tropical abscess of the liver is as clearly the result of dysenteric ulceration as a simple surgical sepsis of the finger may lead to an axillary abscess or septic lesions anywhere in the body.

I have often thought of the question of ischio-rectal abscess and its result in *fistula in ano*. Are we to look on it as an instance pure and simple of focal infection? In many such cases which are tuberculous, there is a tuberculous lesion elsewhere and the rectal infection is secondary. Perhaps, in some the abscess is really the first manifestation of tuberculous infection. I take it that the arrangement of the mucosa above and over the sphincter make just the condition in which an abrasion is easily made by hard fæces and, once made, the ischio-rectal fossa is an excellent field for microbic development. But not all abscesses in the region are necessarily tuberculous; other organisms may easily find their way outside the protecting rampart of mucosa. A crude foreign body like a fish bone may make the breach in quite a healthy subject. But given a feeble resisting power, as in the tuberculous, such a solution of continuity is doubly likely to end in abscess formation. I fancy the truth lies somewhere thus: not all abscesses in the ischio-rectal fossa indicate tuberculosis; in practice if they are tuberculous, they are also the harbourers of a mixed infection and further where they do contain the tubercle bacillus, the lesion may be either a primary focal infection or it may be secondary to infection brought to the rectum from above, either from the bowel itself or from sputum swallowed.

But systemic diseases themselves may lead to focal mischief elsewhere. To illustrate my meaning, I instance enteric fever, the intestinal lesions of which more than possibly may lead later on to a gall bladder infection and

so to gall stones. This is difficult to prove, but clinically I fancy that most of us have a strong feeling that such a sequence does really exist. Certainly such a connexion is suggested in regions not connected with the bowel, by the cold abscesses one sees occasionally in the course of enteric fever.

Our forefathers knew much about the obvious sources and results of focal infection, though I doubt if they used that term and I need not detain you with instancing some of them. It is rather concerning the less obvious, but none the less important conditions in which a focal infection is the starting point of grave consequences, that the clinical observer is now always on the lookout to discover and concerning such, as well as some of those to which I have alluded, is the attention of this meeting directed. And from a discussion upon them I do not doubt much valuable knowledge will be shared among us who are present here to-day.

THE ROLE OF FOCAL INFECTIONS IN DISEASE.

By S. O. Cowen, M.D., M.S. (Melbourne),
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I desire in the first place to express my complete agreement with the opener of this discussion and with subsequent speakers who have emphasized the importance of focal sepsis as a cause of various general disease processes. I think, however, that in this as in other comparatively new conceptions we should from time to time survey the position we have assumed and examine the evidence on which our beliefs rest. As the matter stands at present, proof of the relation between the focus of infection and the general symptoms is empirical and rests on the following evidence: (i.) Absence of any other demonstrable cause, (ii.) failure to cure the symptoms by all other methods of treatment, (iii.) prompt and continued relief without return of the symptoms on the cure or removal of the focus of infection. If these criteria were strictly applied, we should exclude unjustifiably many instances of focal infection. We would, moreover, include cases in which relief was more properly attributable to psychic effects or to the beneficial results of the eradication of sepsis *per se*. We must, I think, admit that our beliefs have not at present a secure scientific foundation.

It is necessary, therefore, that we should inquire into the ætiological and pathological side of the question and ask ourselves by what mechanism remote effects are produced by the offending focus. There are at least three possible modes of action.

Firstly, the distant lesions may be the result of actual bacterial metastases, as, for instance, in subacute bacterial endocarditis. Much more commonly there is no proof of local bacterial invasion; for example, in rheumatoid arthritis attempts to grow organisms from the affected joints are uniformly unsuccessful. It has been suggested that this failure is explainable on the basis that the organisms are few in number and are rapidly engulfed and destroyed by phagocytes, lesions being produced by the liberation of toxins during their destruction. But this is an entirely speculative explanation.

Secondly, the systemic lesions may be due to the action of bacterial toxins liberated in the focus and disseminated by blood and lymph paths. Here again proof is difficult, but may some day be provided by immunologic studies.

Thirdly, the affection of certain tissues may be due to local sensitiveness to bacterial proteins, an anaphylactic reaction. Dale's conception of fixed antibodies lends support to this theory. Perhaps it may yet be possible to demonstrate by means of skin tests, like those employed in asthma, sensitivity to an organism isolated from the focus.

The position is complicated by the fact that more than one of these mechanisms may be at work in any one case. For example, dyspeptic symptoms associated with chronic constipation may be due to actual gastric lesions or may be merely an expression of the general toxæmia arising from the colonic stasis.

Intimately associated with these problems is another and still more difficult question, that of the principle of elective localization. Rosenow's conclusions have hitherto lacked confirmation and much work remains to be done in this connexion.

In conclusion I wish again to emphasize that I do not deprecate the importance of focal sepsis as a cause of general disease. The clinical evidence is much too striking to be overlooked, but it is not altogether conclusive. My remarks have been made, therefore, in no carping spirit, but with a genuine desire that we should prosecute every means of placing this important subject on a firmer and more rational basis.

Dr. F. L. Apperly said that for some months he had been trying to obtain some exact information on the subject of the rôle of focal infection in disease. For this purpose he had used the fractional test meal before and after operation for the removal of one type of focal infection. He regarded this as a convenient method of making exact observations on the effect of the removal of a focus. He had examined about twenty patients prior to the operation of appendicectomy by this method. Records had been kept of the microscopical appearance of the appendix and of the results of bacteriological examination of that organ. With the exception of a few patients whose gastric acidity before operation was high as a result of pyloric spasm, there had been no change in the acidity curve after the removal of the appendix. That meant that the removal of a focal infection had had no effect on gastric function. On the other hand five or six patients with rheumatoid arthritis with joint changes had been examined and in all it had been found that there was either complete absence of free acid or the free acid had been present for about fifteen to thirty minutes only after which neutralization followed. This meant that in these patients there was jejunal hyper-irritability. As previous work had shown that this was probably due to intestinal infection, it suggested that intestinal infection was the source of the arthritis, though, he recognized, the converse might be true. He thought it less likely. In either case it showed how a focal infection might produce changes elsewhere.

Dr. S. Pern had been interested in the paper read by Dr. Scot Skirving. But a few years before the question of focal infections had been regarded as another fad of a few enthusiasts. The eyes of the majority had since been turned to the seriousness of the question. When they realized that in focal infections the bacteria gained an entrance to the blood and lymphatic streams, it would be evi-

dent that no tissues of the body could claim immunity. They knew that certain streptococci had affinity for certain tissues and they would have to admit that there were specific strains for all tissues which were supplied by blood vessels. They should not confine their attention to such conditions as arthritis, nephritis and the like, but should include diseases which attacked every tissue. As the majority of diseases were manifestations of dysfunction of some cells in the presence of focal infections. the most probable cause of dysfunction of the cells would be the organisms from the focal infections. Diabetes, epilepsy, arterial changes, dysfunction of the pituitary and so on should be borne in mind. If they would work along these lines, the clinical results obtained would often be surprising. The President of Congress in his inaugural address had remarked on the extraordinary number of men who had been found to be unfit for service at the time of enlistment. A few years ago, he, the speaker, had compiled statistics from the out-patient departments of the Melbourne Hospital. He had found that between 60% and 70% of all patients attending the medical clinics were suffering from diseases due to the presence of focal infections. This corresponded to the figures of the Mayo clinic. There were three main causes of damage to the human organism, (i.) tuberculosis, (ii.) venereal disease and (iii.) focal infections. The rest of disease was usually transitory and tended to leave the body little the worse for its presence.

Prevention was the key note of the Congress. They asked themselves whether they were able to stamp out this 60% of disease that was filling the hospitals. In the majority of cases they could say that the problem presented no great difficulty, as the majority of focal infections could be easily dealt with. In this connexion they had greater facilities for prevention than in any other line. When they saw a child with gross heart lesions or crippled with rheumatism, they must be impressed with the fact that there were not more children like it. Dr. Pern maintained that they were entering a new era of medicine which was going to bring inestimable benefits to humanity. When they removed a child's tonsils, they not only cured him of some present disability, but they saved him from some gross bodily damage which assuredly would happen sooner or later. They were not agreed as to what tonsillar infection was and it was a debateable point whether or not it was possible for an adult to have an infected tonsil. Culturing virulent streptococci in one's own tonsils was not a pastime that he would recommend to his friends on the slender hope that they would raise their immunity against infections. They were all more or less agreed on the question of infections of teeth, but he would like to urge that even when there were no signs at the roots of dead teeth, this should not be accepted as evidence that these teeth were free from infection. At the Mayo clinic they had found that almost all dead teeth were infected, whether indications were seen on the X-ray film or not. He referred to the work of Rosenow who had injected the pulp cavities of dogs' teeth with streptococci isolated from renal calculi. As a result he had produced stones in the dogs' kidneys. This showed that certain strains of streptococci had an affinity for the production of stones.

Dr. W. N. Horsfall thought that there was such a thing as individual resistance. He remembered a case of puerperal sepsis. The patient had died ten days after her confinement. I heard later that she had nearly died of sepsis during her first confinement. The point was, he thought, that she had a lowered resistance, not only a temporary condition, but a permanent one. Sub-acute bacterial endocarditis had been said to be due to *Streptococcus viridans*. This streptococcus had been found in the blood in persons suffering from this condition. It had been found in teeth sockets. The picture would appear to be complete that this was a condition of a focal infection. Lewis in some late work had stated that the determining factor in the causation of sub-acute bacterial endocarditis was the presence of congenital defects in the heart valves. The presence of the streptococcus was an accompaniment. Any person might have these germs in his blood at various times, but they did not live. To be healthy, they must keep fit.

Professor A. E. Mills asked if, when a focal infection had been present for years and an infective disease arose, they were justified in saying that the former was the cause of the latter. To attribute all infective disease to focal infections was unjustifiable and he thought that there had been too much unscientific reasoning in assigning such a cause to many infections. The ruthless enucleation of tonsils to prevent infections that might never arise seemed to him to be quite unreasonable. The same might be said of extraction of teeth. At one time the dentists' slogan had been: "No tooth is too bad to be saved!" It seemed to have changed to: "If anything is wrong with a tooth, take it out!" Medical practitioners were as much to blame as the dentists in this wholesale removal of teeth. Professor Mills urged that greater tolerance should be exercised in the estimation of scientific facts.

He admitted, however, that there existed certain cases in which it was very probable that certain infections of a general kind arose from a septic focus. He instanced the case of a little girl who had suffered from diabetes and who had had large, unhealthy tonsils, large cervical lymphatic glands and an ulcerative stomatitis. Enucleation of the tonsils had been performed and the child had been dieted. The diabetic condition had disappeared. The child had subsequently had an attack of measles; the diabetic condition had returned, but had disappeared after convalescence from the infection. He held that in any case of tonsillar infection the first evidence would be found in the enlargement of the corresponding lymphatic glands. In conclusion he pleaded for more exact observation and more reserve in expressing an opinion as to the connexion between septic foci and infective diseases. If this were done, he would expect that much unnecessary surgical interference would be avoided.

Dr. W. Marshall Macdonald drew attention to the fact that a patient who was apparently edentulous, might have some septic focus in his mouth. At the Mayo clinic an X-ray examination of three hundred such patients had revealed an infection in one hundred and eighty. He believed that there was a close connexion between infected tonsils and nephritis. Castaigne had called attention to the occurrence of abnormal pharyngeal conditions in patients with nephritis. Dr. Macdonald had rarely failed to obtain some history or evidence of focal infection in patients with nephritis. In all conditions of general infection a skiagram of the teeth should be obtained and if a pathological condition, such as an apical abscess, were detected, that tooth should be removed. He mentioned the observation of Rosenow on the production of gastric ulcer from a purulent focus as being worthy of notice.

Dr. Val Macdonald said that he would like to urge the importance of dental conditions in relation to septic foci and systemic effects. In the presence of both gingival and apical lesions systemic conditions might be found coexisting and removed or alleviated by treating the sup-

posed causal factor. He had seen a patient with severe myocarditis show rapid improvement by treatment of a necrotic condition of the right side of the maxilla. In this case the heart gave immediate evidence of a collection of pus in the necrotic area and was rapidly relieved by its removal. In another patient with myocarditis attention to a pyorrhœal condition and treatment with a mixed autogenous vaccine gave a quite remarkable result. Again, in a long standing case of a low grade type of iritis the patient's oculist said that if the patient had been in hospital he would have regarded it as specific. But removal of three abscessed lower teeth and the use of a mixed autogenous vaccine had brought about rapid improvement.

There were many factors to be considered and research work upon the bacteriology of the mouth was only then being taken up seriously. Goadby had blazed the trail and induced others to closer study of it, so that they had recent valuable additions to knowledge contributed by Rosenow, Hartzell and others, including Glynn, of Liverpool, and the future held promise of a far better knowledge of the bacteriology of the mouth and of the pathogenicity of the organisms found therein. The rôle of septic accessory sinuses and tonsils must not be forgotten. They had much to learn of the ductless glands and of their influence in assisting the body to resist disease. He pleaded for restraint in the sacrifice of suspected teeth, for they should realize that dental science had made sufficient progress to justify such a plea and to allow of conservative efforts frequently to score success. Rosenow had claimed a definite elective localization for streptococci in dental lesions and there was probably much truth in his claim, though other workers maintained that he claimed too much. They should not forget that a lowered line of resistance in any tissue might be a determining factor in the nature of the systemic attack. It would appear that streptococci were the chief pathogenic organisms in these foci in and about the teeth, but he had noticed the frequency with which diphtheroid organisms occurred in cases in which the systemic condition has been of a rheumatoid character. This might have been a coincidence; their pathogenicity had not been proved. In one case of an acute pyorrhœal abscess an almost pure culture of spirochætes had been obtained. It did not require a gross septic condition in the mouth to produce a systemic effect. It was quite sufficient to find a persistent definite focus and a lowered general resistance without a gross focus.

The mass of clinical evidence left no doubt that a definite relation might exist between a septic focus about the mouth and a general or systemic condition. They should not jump to conclusions. For instance, a mass of salivary calculus did not necessarily mean a pyorrhœal condition. A dental confrère had assured him that on one occasion a patient had been sent to him for the treatment of a pyorrhœal condition, but he had found the patient edentulous and wearing full upper and lower dentures.

X-ray examination was valuable both as an aid to diagnosis and to watch the result of conservative treatment. This had been shown in an excellent paper recently published by Dr. Menzies, of Brisbane.

In conclusion when extraction was indicated, the mouth should be cleared up first and as an extra precaution against a too severe reaction, it was a good plan to give one or two doses of a mixed autogenous vaccine before any extractions were undertaken. Too many teeth should not be extracted at one time. Finally he had made a practice of swabbing the sockets after extraction with pure "Lysol" partly to lessen absorption and partly as an obtundent.

THE AETIOLOGY OF GOITRE.

By Sydney Pern, M.R.C.S., L.R.C.P.

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The thyreoid gland is one of a group making a complex system. Dysfunction of any part of it will interfere with the action of each of the other individual parts. It is what we now understand as that of regulating matters of self-preservation, propagation of species and the acquiring of food. The chief factors concerned in this group are the thyreoid, adrenals, sympathetic nervous system and pituitary gland. These are so intimately connected that interference with the action of one is reflected on each of the others and incidentally will produce signs of hyperfunction or hypofunction of the thyreoid.

The cogs in the goitre mechanism which are liable to variations and require explaining, are the following: calcium, iodine, variations of thyreoid colloid, variations of viscosity and coagulability of the blood, vaso-dilation, systemic and localized infections in the body, infections of the thyreoid, growths within the thyreoid, interference with the normal action of the adrenals and sympathetic nervous system, local irritation and infection of the sympathetic ganglia, factors interfering with the manufacture of thyroxin, retention of the colloid within the tissues as in myxœdema, and lastly heredity. It is probable that the thyreoid is influential in converting the free calcium ions into some colloidal form which is essential to the body needs.

The prevalence of goitre in limestone districts is an outstanding fact and the goitres are usually accompanied by signs of hypothyreoidism. The goitres tend to be large with a retention of colloid; cretins are often the progeny of persons with goitres. They are invariably relieved by the exhibition of iodine and cretinism can be prevented from developing by the exhibition of iodine.

Many colloids owe their degree of viscosity to the balance between the amount of iodine and calcium they contain. Applied to colloids, such as blood, milk, egg albumin or gelatine it will be found that the addition of iodine reduces the coagulability, whereas the addition of calcium increases it.

Goitres in these areas we now know are deficient in iodine and from these premisses we should naturally expect to find the body colloids of people with goitres to be more rigid than others.

This is exemplified in persons suffering from myxœdema, whose tissues are clogged with a viscid colloid which vanishes under the influence of iodine. Do we not find in thyreo-toxic goitre the viscosity of the blood very much diminished and all symptoms of increased iodine output, together with a reduced coagulability of the blood? All this suggests calcium starvation by increased excretion or reduced intake.

Such also suggests that myxœdema is calcium retention owing to lack of iodine to bring about its excretion.

We do know that there is usually plenty of iodine near the sea coast due to decomposition of seaweed and that green food contains a certain amount. That goitre with deficiency or apparent deficiency of iodine is so associated

with limestone districts strongly suggests that the calcium in some way fixes the iodine and so leaves insufficient for proper body metabolism or that larger quantities of iodine than normal are needed where the intake of calcium is excessive. That iodine is necessary for the excretion of calcium is rather borne out by the fact that in all cases of increased thyreoid activity there is also an increased excretion of calcium.

Having found symptoms suggestive of calcium retention in the goitrous people of limestone districts where hypothyreoidism is dominant, one would expect the reverse in cases where hyperthyreoidism pertains. Some years ago in South Gippsland, where there was much goitre with thyreo-toxic symptoms, I was struck with the frequency with which one came across *post partum* hæmorrhage. I might also add that this district is very deficient in lime and quite close to the coast, thus insuring adequate iodine. I began to treat the patients with calcium lactate and soon found improvement and I ceased to get *post partum* hæmorrhage. Research work in the past has shown there is an increased output of calcium in thyreo-toxicosis. It is well known that in prolonged diseases such as tuberculosis there is a demineralization of the tissues. Most chronic infections are associated with increased thyreoid activity and that results in increased calcium excretion. Nature has equipped the thyreoid as the storehouse for iodine to be used as required. It is in the form of a colloid and to be available must be of a certain rigidity.

In goitres of limestone districts the vesicles are unduly distended with unavailable colloid which is brought into use by the administration of iodine. Contrast this with thyreo-toxic goitre, in which there are all signs of iodism with empty vesicles and a thin colloid. The colloid, being so thin, is constantly being poured into the system whether it is needed or not. There is hyperfunction in both cases; in the one the colloid cannot be used and in the other it cannot be stored.

It may be possible for the tissues to be saturated with calcium and the blood to hold diminished quantities. We are probably faced with some such condition in myxœdema. The results of some work done by Marie Parhon tends to bear this out. The crux of the goitre question seems to turn on this balance between the calcium and iodine and their relation to colloids. It explains the principle of myxœdema, the cause of reduced viscosity and reduced coagulability of the blood in thyreo-toxic cases. It explains the cause of endemic goitre in limestone districts and the cause of thyreo-toxic goitre near the coast and where lack of calcium is present. It seems to fit into and show the link between thyreo-toxic and endemic goitres of limestone districts. From whatever aspect goitre is looked at, these two factors will always be dominant. Yet they are only contributing agents.

Turning to the defence mechanism of which the thyreoid is a part, we shall see that interference of any portion of this system is reflected on the functioning of the thyreoid.

The visceral changes in fear and anger are alike. The influence of shock and nerve strain in the production of thyreo-toxic goitre must be stressed. It is well recognized that sudden strong emotional stress and prolonged severe nerve strain arouse the whole defence mechanism, causing a tremendous output from the thyreoid, adrenals and pituitary; indeed many of the manifestations of anxiety neurosis are identical with those of thyreo-toxic goitre, as has been exemplified so particularly in war neurosis.

In practically all these cases infected tonsils, sinuses or some other focus could be found. These men at the time of enlistment showed no constitutional symptoms, yet when such were exposed to all the hardships, strain and fatigue of war, they were the first to break down.

Patients with goitres who manifest no thyreo-toxic symptoms to speak of, will develope them if mental worry is superimposed. The same class of shell-shock symptoms can be seen in those who have never been to the war, yet who have marked focal infections and do not necessarily present any enlargement of the thyreoid. This is also explainable.

It is now obvious that strain, as is imposed during a railway accident, can produce symptoms of exophthalmic goitre in a person already suffering with a chronic infection. I do not doubt the possibility of it developing under severe nerve strain alone.

From the foregoing it is obvious that the defence mechanism, if attacked from any quarter, will depict the same class of symptoms.

These, I depicted in 1919 under the designation of the toxic syndrome.

A normal thyreoid will be able to meet almost any demands thrown upon it without enlargement, but as soon as it is unable to supply the proper ingredient, hyperplasia will begin; thus we get signs of hyperfunction without enlargement as well as hyperfunction with enlargement.

We cannot exclude the possibility of the thyreoid being invaded by organisms of low-grade virulence.

Thyreoid enlargement will also occur with general systemic invasion if its colloid is at fault.

As the result of some recent work I have found that in thyreo-toxic goitre there is a reduced viscosity by as much as 25%. This together with reduced coagulability strengthens the idea of an impaired calcium metabolism.

That some cases of thyreo-toxic goitre are associated with exophthalmos and others are not requires explanation. I have lately had five patients with extreme exophthalmos, two of whom had practically no thyreo-toxic symptoms. As they all had the same exciting cause, the presentation of one case will explain the whole.

Miss E. M., *aetatis* thirty-seven years, was operated on for exophthalmic goitre thirteen years ago. Her general thyreo-toxic symptoms were improved, but not her exophthalmos. For the last seven years she has been unable to close her eyes owing to the extreme degree of protrusion. This resulted in a constant state of inflammation of them. She also had diplopia. She had severe and persistent headaches and on careful questioning it was found that there was a good deal of yellow post-nasal discha[illegible] Within a week of putting her on treatment for her infected sinuses, the headaches ceased, the diplopia vanished and the eyes began to recede. The eyes have receded steadily and within three months have almost returned to normal. In proportion to the amount of improvement of the sinusitis, so will the exophthalmos improve.

Lesion or irritation of the superior cervical ganglion will affect motor and secretory cells in the muscle of Müller, the thyreoid and the heart; lesion of the median

ganglion will affect the thyreoid and the heart; lesion of the inferior will affect the heart alone.

Evidence of direct infection of the cervical ganglia have occasionally been found *post mortem*.

Pottenger showed how in phthisis afferent nocuous impulses passing from the lung to the cervical portion of the cord, set up irritation in the neighbouring nerve cells; the efferent impulses from these resulted in increased tone of muscles, wasting and atrophy of tissues. The same mechanism must be applied where infected sinuses are concerned, causing increased tone of Müller's muscle and with the added irritation of the superior cervical ganglia from this source, tachycardia with increased thyreoid output would result. So cervical ganglia irritation is possible from a direct as well as an indirect source. In cases showing marked exophthalmos, particularly where one eye is more prominent than the other, sinus infection is almost sure to be found. Again with tonsillar infection the indirect irritation of the cervical ganglia is probably responsible. We must at the same time realize that the irritation of the general sympathetic nervous system may be so pronounced as to produce some exophthalmos in infections remote from any possibility of irritating the cervical ganglia, but under such conditions we are far more likely to find thyreo-toxic goitre without marked exophthalmos. This does not explain the deposit of orbital pad of fat which is usually found in such cases.

Experiments by Marine and Lenhart showed that a goitre cannot be produced in an animal if the thyreoid is kept saturated with iodine, whereas, on the other hand, if an animal is deprived of iodine, the thyreoid will start to enlarge as soon as the iodine content gets below 0.1% of the total amount of dried gland tissue.

As acquired characteristics are not usually transmitted, this requires some explanation. McCarrison mentions that if a large portion of thyreoid of a pregnant bitch were removed, the pups were borne with goitres. During pregnancy and for some months after the pups are dependent upon the mother for the necessary thyreoid secretion, which is delivered to them in the milk, as their own thyreoids are only partially or not functioning at the time. The removal of a large portion of the mother's thyreoid deprives the pups of the needful thyreoid secretion, so their own thyreoids endeavour to meet the demands by becoming hypertrophied.

Recently great stress has been laid on the deficiency of iodine and its part in goitre, so much so that it seems to have swamped out every other element. Goitre is very prevalent in Southern Gippsland which is coastal and hence supplied with adequate iodine, also the majority of patients manifest varying degrees of hyperthyreoidism. So we must realize that iodine shortage is not the only factor in the goitre question.

Given a community on a small iodine ration, as long as no great demand is made on their thyreoids, they will have enough to carry on with, but throw an extra strain on the gland and the available colloid will quickly be exhausted; then hyperplasia will set in. Hence those with infected tonsils or sinusitis will be the first to show signs of thyreoid enlargement. Treating goitres for many years has shown me that such endemic goitres are very little influenced by iodine treatment alone, but on the complete removal of the infecting agent 10% of the patients get well. I particularly wish to emphasize this point, as there seem to be undue optimism in the generalized iodine treatment at the present time. If this was the sole cause of goitre, iodine would banish goitre, whereas we know it only reduces its incidence. A bottle of volatile iodine left uncorked in the schoolroom will be as efficacious as the administration in tabloid form. Infections in goitre are that the inciting agents in the majority of goitres of all types, and other conditions are subsidiary to them.

As infections bring the defence mechanism into action, it is quite obvious that the type of infecting agent is only a secondary consideration. This is well illustrated by the work on goitre by McCarrison in India where an intestinal bacterium was found to be responsible. In Brazil Dr. Carl Chagas found that goitre was due to a trypanosome. Marine and Lenhart found that trout bred in crowded hatcheries developed goitre. Rupert Farrant and I about the same time came to the conclusion that goitre was due to the presence of bacterial infections. These are usually located in the tonsils, nasal accessory sinuses, around or at the roots of teeth, appendices, gall-bladders, tubes *et cetera*. It is the lack of the complete removal of such that leads to failure and makes men condemn the principle.

Faults in the metabolism of thyroxin may be influential in producing goitre.

Dr. W. Marshall Macdonald recommended the administration of iodine to school children as was being done in New Zealand. As to influences at work in producing Graves's disease he instanced the case of a young woman suffering from this disease who had been found to have insomnia and dreams which had been suppressed. Attention to these had been followed by a decided amelioration of her symptoms. Toxic adenomata of the thyreoid gland should be treated by operation. The danger of operation in exophthalmic goitre was that it was frequently undertaken by an unskilled surgeon.

He would be a bold physician who would advise only medical treatment when success had not been attained by this means, but medical treatment should precede an operation.

He had obtained improved results from X-ray therapy. He thought that radio-therapy offered a safer method of treatment than surgery and suggested a closer cooperation between the surgeon and the radiologist, the surgeon to remove less gland and to follow this up with radio-therapy.

Dr. Sydney Jamieson referred to a patient with exophthalmic goitre from whom an infected tooth was removed and the patient put on a vegetarian diet. This had been followed by slow recovery. This patient's brother had also developed Graves's disease.

Dr. Terence Butler remarked that at Zeehan, Tasmania, the water supply was from rain water tanks and that the water therefore contained no calcium. Goitre in this district was very prevalent. Experience at Zeehan, therefore, did not support the theory that goitre was dependent upon an excess of calcium in the blood.

He had administered iodine for seven years in Hobart to all patients with goitre and found that about 98% had

been cured. He always treated patients with hyperthyreoidism by the exhibition of calcium and had experienced beneficial results. Three patients affected with severe hyperthyreoidism, who were resistant to calcium, progressed very well upon a combination of calcium and small doses of arsenic.

Dr. Gifford Croll said that the theory that goitre was dependent upon calcium excess and iodine deficiency, whilst it had much in its favour, could not be accepted as entirely satisfactory. Experiments had shown that fish placed in water from a goitrous district developed goitre, but if the water was sterilized and more fish were placed therein, such fish did not develope goitre. Also, fish placed in rain water heavily contaminated by faecal matter developed goitre. There might be some relation between the presence of septic foci and the occurrence of goitre.

Dr. Pern had referred to the intimate relations between the sympathetic nervous system and the thyreoid, adrenal, and pituitary glands. Theories based on such relationship had been frequently advanced, but he did not think that they could yet be accepted as proved. The adrenal was closely related to the sympathetic nervous system in the medullary portion of the gland, but in fish the adrenal medulla had been successfully removed without serious disturbance of the thyreoid or subsequent serious effect upon the fish. The same applied to the posterior lobe of the pituitary gland which had been successfully removed from animals.

In his reply Dr. S. Pern said that there was two things pre-eminent in what all the previous speakers had had to say. The first was that all were agreed that the only treatment for exophthalmic goitre was operation. The second was that there was an acknowledgement that absolutely nothing was known about the cause of this kind of goitre, as not one word had been said as to the removal of any possible cause. Such being the case they must then realize that all treatment put forward was entirely empirical. He was not in agreement with the previous speakers. He agreed that operation was necessary in a small number of patients, operative treatment. Although many might not agree with his views as to the infective origin of goitre, he wished them to be of an open mind on this point and not to put it aside as unworthy of consideration. There was one point on the question of exophthalmos which he would like to mention. He had treated five patients with severe exophthalmos; two had previously been operated on. They had all suffered from sinusitis. Three rapidly improved on having the sinus infection treated. One had double antrum disease; the operation was being postponed. The other had previously had so many nasal operations that she was unwilling to undergoing any more. There was a reasonable explanation for this. Pottenger had shown that in tuberculosis the afferent nocuous impulses passing from the diseased lung to the cord set up irritation in the neighbouring cell whose efferent impulses passed to the sterno-mastoid and other neck and shoulder muscles and caused at first spasm to those muscles and later atrophy. They should apply this same mechanism to the harmful impulses passing from the infected sinuses, causing increased tone to Müller's muscle and irritation of the superior cervical ganglion. This explained why exophthalmos was seen so seldom in persons with true adenomatous goitre. As optical demonstration was worth more than much talking, he invited those who were interested, to see his patients at St. Vincent's Hospital. Several had relapsed after operative treatment and had become quite well under treatment, the principles of which he had roughly indicated.

EXOPHTHALMIC GOITRE AND TOXIC ADENOMA OF THE THYREOID GLAND.

By Alan Newton, M.S. (Melbourne), F.R.C.S. (England),
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It is fitting that a paper on this subject should begin with an acknowledgement of Dunhill's work. It is perhaps not generally recognized that he has conferred a double benefit on his successors. Not only has he elaborated and successfully practised a technique with which the surgical treatment of very bad cases of exophthalmic goitre is successful, but also this success in such cases has resulted in bringing many patients to operation at an earlier stage, thus making the task of the surgeon easier.

In this series there are forty-nine patients with exophthalmic goitre comprising sixty-one operations and thirty-five patients with toxic adenoma with thirty-five operations. These patients have been treated since January, 1920. They are consecutive and in no case has operation been refused. The cases of toxic adenoma have been included because many of them presented surgical problems which were comparable to those encountered in the exophthalmic goitre series. All the cases described as exophthalmic goitre presented the characteristic clinical findings.

In the present series there has been one death. This occurred in the first patient operated upon and was due to faulty technique at the operation, in that too much blood was lost. The patient died of hyperthyreoidism in two days. After this fatality I had the opportunity of watching Dunhill at work. I have since followed his methods and in sixty consecutive operations there have been no deaths. As will be described later the chief secret of success lies in the prevention of hæmorrhage. This can only be achieved by the use of a very large number of bæmostatic forceps. The surgeon should have at least one hundred of them. All tissues should be divided between forceps. After the removal of the gland a small forest of artery forceps projects in the wound. It is very necessary to employ a great number of forceps, for it is wrong to clamp a large amount of tissue at one time, since the ligature may slip and cause reactionary hæmorrhage. No such accident has occurred in this series. It may be justly claimed from these figures that, if proper methods be employed even by a beginner in thyreoid surgery, the operative mortality of exophthalmic goitre is small.

There were no deaths in the toxic adenoma series.

Some authorities ascribe the reduction in the mortality figures of thyreoidectomy to the use of local anæsthesia.

In this series ether anæsthesia has been employed for all patients but one in whom a toxic adenoma was complicated by pulmonary tuberculosis and in whom, therefore, local anæsthesia was adopted.

Injury to the recurrent laryngeal nerve is an important risk in the surgical treatment of goitre. Routine pre-operative and post-operative laryngoscopic examinations should be made. It is occasionally found before operation that a unilateral paralysis due to pressure of the gland is present. If this be unrecognized and a partial thyreoidectomy be performed on the opposite side,

there is a risk of injuring this nerve also and thus producing a bilateral paralysis which is a tragic complication.

Dr. Frank Andrew has been kind enough to give me the following details of his experience of recurrent nerve palsy after thyreoidectomy. Among one hundred and fifty patients examined after operation he found in twelve unilateral recurrent paralysis without disability. In four others there was a more complete lesion of one nerve resulting in atrophy of the vocal cord. This condition causes serious disability in that the patient is unable to cough and so tends to drown in the bronchial secretions when infections occur. All these patients were relieved by paraffin injections of the atrophied cord. In four others bilateral recurrent paralysis was present. These patients suffered from great dyspnœa and cyanosis. In two of them an emergency tracheotomy was necessary. Two have died, a third is awaiting operation for cord transplantation, whilst in the fourth this step is contra-indicated by cardiac degeneration due to the dysthyreoidism. It will thus be realized that a bilateral recurrent paralysis is a very serious complication.

Searby has recently investigated the course of the recurrent nerve in twenty-four cadavers. He has found a considerable variation in the relation of the nerve to the inferior thyreoid vessels. In only 50% were both nerves in such a position that for all practical purposes they were safe from injury. When the nerve lies ventral to the inferior thyreoid artery, that is between this vessel and the gland, it is inevitably subjected to some tension when the lateral lobe is delivered. This slight traumatism is sufficient in some cases to cause a transient paralysis. This accident is not of great importance as the loss of function rarely lasts more than three months, but it will be obvious that it cannot be avoided even by the most careful surgeon. Searby found that this relation to the artery was present on one side in 42% and on both sides in the remaining 8%.

In this series a transient paralysis was produced in four patients and in one a more permanent paralysis without cord atrophy and therefore without symptoms is present. No case of bilateral paralysis occurred in these patients.

In two cases a pressure paralysis of the nerve was found before operation and in both this paralysis had disappeared in a fortnight after the gland had been removed.

It cannot be too strongly emphasized that removal of one lobe, the isthmus and perhaps a small portion of the opposite lobe is not sufficient to do more than to effect an improvement in bad cases of exophthalmic goitre, though it may suffice in milder cases. Dissatisfaction with surgical results is usually due to an inadequate removal of the gland. Cure in some of the worst cases in this series was not achieved until all the gland, except a portion at one upper lobe about the size of a thumb nail, had been removed. To achieve this end a two-stage operation is necessary.

Hector Mackenzie has stated that: "the presence of auricular fibrillation made one hesitate to advise operation, but on occasion risks had to be taken" and he sometimes felt that the risk was worth taking.

The experience gained in this series goes to prove that operation is strongly indicated in these patients and that the presence of this complication does not increase the operative risk to any appreciable extent. The excellent results of combined medical and surgical treatment of auricular fibrillation due to this disease have been described by **Dr. Turnbull.**

Some of my earlier patients with severe symptoms had been subjected to prolonged X-ray treatment and though the difficulties of operation were increased by adhesions, the post-operative course was smoother than had been anticipated. These cases led me to the conclusion, based entirely on clinical observation, that after X-ray treatment the post-operative risks were lessened and in this belief pre-operative X-ray treatment has been carried out in many of the patients.

I am not competent to offer an opinion on the value of X-ray treatment as a substitute for operation as I have only seen patients in whom the result of X-ray therapy was unsatisfactory and for whom, therefore, thyreoidectomy was advised.

As all these patients have been operated upon during the last four years it is perhaps too early to base an adequate estimate of the results of surgical treatment upon them.

Twelve patients in this series have had more than one operation. Eleven of these had a two stage removal of the gland and in one three operations were performed.

Nine of these patients have recovered completely and have been able to return to a normal mode of life. One man has been able to resume control of a large business and another, a medical practitioner, states that he has recovered completely and is now engaged in active practice in the country.

Two patients in this group had corneal ulceration resulting in one in the loss of both eyes and in another in serious interference with vision. The signs of dysthyreoidism disappeared after operation in each case, but the result is unsatisfactory for operation was too long delayed and was ineffectual as far as the exophthalmos was concerned.

In the last patient who required three operations, though great improvement has resulted, surgical treatment has not produced a complete cure. This is to be explained by the fact that owing to faulty technique in the first two operations removal of an adequate amount of the gland was not possible at the third stage.

In the remaining thirty-seven patients one operation has been performed. In eight of them signs of dysthyreoidism were present and removal of one lobe, the isthmus and a small portion of the opposite lobe has produced a considerable improvement in the signs, but a further operation will be necessary as sufficient gland has not been removed to achieve a cure. The remaining twenty-eight patients were sufficiently improved by one operation. In the majority it was possible at one stage to remove two-thirds of the gland and as yet no relapse has occurred in any of them. They are able to enjoy life and are quite satisfied with the results of the operation.

No case of hypothyreoidism as a result of removal of too much of the gland has been observed in this series.

There is always a striking improvement after operation and, if this is not maintained, the explanation is that an inadequate removal has been performed.

Table I. summarizes the results in this series.

TABLE I.

Result of Treatment	Operation	
	Two Stage	One Stage
Cured	9	20
Much Improved	1	8
Improved	2[1]	8[2]
Not Improved	0	0
Died	0	1
Total	12	37

[1] Recovered with loss or impairment of vision.
[2] Awaiting further operation.

I have endeavoured to describe as impartially as possible the risks of surgical treatment as regards immediate mortality and later disablement such as follows division of one or both recurrent laryngeal nerves. Two patients have also been mentioned in whom surgical treatment failed to prevent the development of serious eye complications.

Although it cannot be denied that many patients with exophthalmic goitre recover after medical treatment alone has been employed, for the natural course of the disease is to progress by a series of remissions and exacerbations towards cure, yet it appears that the mortality among patients which have not been subjected to operation, is greater than is commonly acknowledged and that many of the survivors are reduced to a condition of chronic invalidism by severe visceral degenerations. Another objection to medical treatment is that few patients for economic reasons can afford the time necessary to achieve a cure by this means and that a still smaller number possess the intelligence necessary to carry out efficiently the instructions of the physician.

My own experience of X-ray treatment is not of value in that I have seen only the failure. I have indicated its usefulness as an adjunct to surgery.

My belief is that in the present state of lack of knowledge of the cause of exophthalmic goitre surgical removal of an adequate amount of the thyreoid gland is the surest method of cure.

In the hands of a surgeon who has made himself familiar with the special technique required, this method is not accompanied by a mortality comparable to that which results from other methods of treatment.

Toxic Adenoma of the Thyreoid Gland.

It is only recently that the toxic signs produced by an adenoma of the thyreoid gland have been recognized. Plummer's work in this respect is well known. He has pointed out that many of these cases are regarded as primarily cardiac, the causal relationship of a small thyreoid adenoma passing unobserved. In ten cases in this series diagnosis had been so delayed that severe cardiac damage had resulted.

Auricular fibrillation was present at the time of operation in eight patients and in many of the others attacks of paroxysmal fibrillation had occurred.

One patient, a female aged twenty-five years, was of interest in that an adenoma which had been noticed for six years, began to produce toxic signs after iodine had been injected into it. The activating stimulus of iodine has been pointed out by Plummer and others. At the operation the technical difficulties were increased by a layer of dense fibrous tissue six millimetres in thickness surrounding the right lobe of the thyreoid. In this lobe was an adenoma which macroscopically and microscopically appeared unaffected by the injections.

There were no deaths in this series despite the advanced cardiac degeneration present in many patients.

There can be no question that the treatment of this condition is surgical removal of the adenoma.

Table II. summarizes the post-operative difficulties in ninety-eight patients with exophthalmic goitre and toxic adenoma.

TABLE II.—RESULTS OF OPERATIVE TREATMENT.

Total Operations	Deaths	Nerve Injury		Hæmorrhage after operation	Pneumonia	Other complications
		Transient	Permanent			
98	1	4	1	0	1	2 (superficial stitch abscesses)

PROFESSOR A. E. MILLS defined the present state of their knowledge in regard to the pathology of the disease. The special characteristic of exophthalmic goitre was a hyperplasia of the epithelial lining the vesicles of the thyreoid gland. The cells lost their cuboidal form, hypertrophied and became columnar. He referred to certain form of colloid goitre in which hyperthyreoidism existed. In these cases there was no exophthalmos. He suggested that in the exophthalmic form the goitre represented a response to certain stimuli. The goitre was characterized by an intense vascularity and by a lowering of the iodine content. Professor Mills dealt with the significance of thyroxin and the developement of hyperplasia of the gland and asked whether the stimulus which led to the hyperplasia, acted through the nervous system or depended on a hormone. Cannon's work in suturing the phrenic nerve to the cervical sympathetic chain and Wilson's experiments with the electrical stimulation of the cervical sympathetic supported the latter view, while the result of administration of thyroxin on colloid goitre seemed to favour the former. The principles underlying the treatment of exophthalmic goitre were to given an abundance of food of high calorific value and to insure absolute rest. Medicinal treatment was of little avail. In severe cases the best results were obtained from surgical interference. He expressed a doubt whether the results obtained in this way were permanent.

PROBLEMS IN THE TREATMENT OF EXOPHTHALMIC GOITRE.

By H. B. DEVINE, M.S. (Melbourne),

Honorary Surgeon, St. Vincent's Hospital, Melbourne.

THREE hundred patients with definite toxic goitre operated on over a period of ten years have been selected for study for this paper; doubtful and border-line cases have been eliminated.

My interest in this subject has been inspired by close

association with Mr. T. P. Dunhill, my former colleague on St. Vincent's Hospital, and naturally many of my methods and principles of treatment are coloured by his teaching.

In all case histories an attempt was made to elicit any factor which might be considered a contributing cause in order that, if possible, this might be eliminated by treatment. A brother and sister in a family, seventeen and eighteen years of age respectively, and in another family a girl of twenty and her mother, developed very acute toxic goitre at the same time, suggesting a common cause in each family, but this could not be ascertained. It was a striking fact that very many goitres followed gynæcological causes, adnexal and ovarian uterine diseases or a pregnancy. Occasionally the goitre followed on operation for these diseases or an ordinary surgical operation. Others were a sequence of war bereavements and anxieties or anxious vocations. Focal sepsis was often present, but its ætiological significance was difficult to gauge because it may have been causal or it may have gained a footing in the body because of the depression of resistance consequent on the goitre. Often surgical treatment depended on a question of diagnosis in obscure cases. In our series the following pathological conditions caused confusion.

(1) An acute toxic state in a patient which developed with a dry brown tongue almost like a typhoid condition, with only suspicious signs of thyreoidism and no thyreoid enlargement.

(2) Cardiac conditions; hyperthyreoidism in patients over forty-five had a tendency to cause established or paroxysmal auricular fibrillation. Frequently so chronic was the thyreoidism and so insidious its onset, that it was not uncommon for this cause to remain unrecognized. A man of fifty developed a paroxysmal tachycardia and auricular fibrillation. It was nine months before obvious signs of thyreoidism showed themselves, but by this time the myocardium had suffered serious damage. When the possessor of an apparently so-called "innocent" goitre of long duration developes cardiac disease, it is our experience that thyreoidectomy benefits greatly or cures the heart lesion, even though there are no very obvious signs of chronic hyperthyreoidism.

A very broad review of my series would make me approach the surgical problem of toxic goitre from a practical point of view in four groups, because in each group the surgical management, the apprehension of danger, the amount of thyreoid gland to be removed and the result of the operation vary.

Fulminating Type.

The fulminating type is probably due to acute dysthyreoidism. The thyroxin is produced so quickly that it is poured into the blood in an insufficiently iodized state (Plummer). These patients are often young, between seventeen and twenty-five years of age. The attacks may be acute exacerbations of the ordinary type. The history is often short, the progress rapid and the toxæmia acute. The size of the thyreoid may not be great, but it is intensely vascular and cellular and there may be intense exophthalmos with ulcerating cornea, necessitating an emergency operation in order to save the sight. There is the usual nervous syndrome with intense irritability. There is no obvious cause and the patients require great surgical care. The danger after operation is acute thyreoidism, which is really more of the nature of a dysthyreoidism. There is a great tendency for the thyreoid to grow again. It is necessary that the maximum amount of thyreoid should be removed as soon as practicable and these are the cases in which multiple operations are often needed. It is perfectly obvious that these patients could never be treated by the physician.

Ordinary Type.

The second group embraces the ordinary type which may be acute and will nearly always be surgical, but sometimes may be sub-acute and might then lend itself to a certain amount of medical treatment. In this group the disease runs a milder course. There is generally a definite thyreoid enlargement. This type very often occurs in the child bearing period and may follow some gynæcological cause or a pregnancy. The patients are very much better surgical "risks" and with operation any subsequent thyreoidism is much more manageable. There is not such a tendency for the thyreoid to regrow and the patients are generally cured by an adequate removal of thyreoid in one or two stages. Surgical management, though anxious, is generally successful; this type forms a contrast to the fulminating, in which there is no very obvious contributing cause and the problem of surgical treatment is much more serious.

Chronic Exophthalmic Goitre.

The third group might be called the chronic exophthalmic group. It comprises long-standing affections in which the thyreoid may be said to have burnt itself out; so-called medical cures or goitres that have occurred in early life and have been cured but have recurred in later life or instances of natural cure. They exemplify changes with transient intermittent or constant auricular fibrillation. Gross symptoms of hyperthyreoidism may appear late in the disease and thyreoid enlargement may or may not be a feature. The danger after operation is not thyreoidism, but auricular fibrillation. The result is often unexpectedly good and it is not necessary to remove so much thyreoid gland. In this type of cases there was a great deal of apprehension and anxiety in the surgical treatment, because the myocardium of the patients seemed to be too badly damaged for any operation which involved the removal of only a degenerate gland, but in our experience they did remarkably and unexpectedly well. For example, a patient, fifty years of age, had exophthalmic goitre for six years and for the last six months he had been bedridden, with very severe visceral changes, orthopnœa, ascites, pleural effusion, œdema of the extremities, uncountable and irregular pulse and very dilated heart, but no albuminuria. This patient had had X-ray treatment with no effect. A sub-total thyreoidectomy was done under local anæsthesia and the operation seemed a forlorn hope, but contrary to expectations his medical attendant, Dr. Rodway, wrote to say that his improvement has been remarkable. This case shows that no matter how bad the visceral changes are in patients with old standing exophthalmic goitre, the question of surgical operation should at least be considered.

Adenoma with Hyperthyreoidism.

The fourth group, adenoma with hyperthyreoidism, may be contrasted with the third group and may be called the chronic non-exophthalmic group. There is the same slow output of thyroxin as in the third group, but the patient has had a large "innocent" adenomatous goitre for many years. As a rule, there are distinct visceral degenerate changes with a mild picture of hyperthyreoidism and with no ocular signs. With operation the results are good and the amount of thyreoid resected in proportion to the size of the thyreoid need not be very great. In this group there is no outstanding problem or difficulty in treatment as in the other groups.

Surgical or Medical Treatment.

As you know, exophthalmic goitre is a disease the peculiarity of which is that it is subject to remissions. It is, therefore, difficult to estimate the value of any treatment unless a considerable time has elapsed. About 30% to 50% of the patients who were operated on in our clinic had been under medical treatment. Many of these had got steadily worse. Others were sent for operation because they had reached a standstill stage; in quite a number the disease had recurred in later life or even a short period of years after apparent medical cure and operation was necessary.

Medical treatment is faced with the facts that it is only applicable to a certain type of case, that cure is most uncertain, that recurrence at any time is likely, even after apparent cure. As I have pointed out, chronic thyreoidism is so insidious and almost silent in its effects on the heart that we dare not risk its effects for very long. In St. Vincent's Hospital bed room is scarce and goitre has come to be regarded as a surgical disease. Our hospital patients are therefore operated on early in the disease. In these we notice that the restoration to health and, what is almost as important, to work is very quick, whereas in our private work, because of the fear of operation and because the patients can afford to rest and have medical treatment, they come at a later stage of the disease and we find that after operation restoration to health and to work is very much slower.

A patient with exophthalmic goitre should have medical treatment while there is improvement, as a preliminary to surgical operation. Efficient medical treatment reduces very much the risk of any surgical procedure, while incomplete cure in many instances after surgical treatment is due to the fact that medical treatment has not been persisted in after the operation.

It is of great importance that the surgeon should choose a propitious phase in the disease and that exacerbations, which are characterized by great loss of weight, restlessness, rapid pulse, high basal metabolism and crises of vomiting and diarrhœa, should be avoided. The mere percentage of basal metabolism alone is not an indication as to operation, but must be taken in conjunction with the symptoms, particularly loss of weight.

X-ray Treatment.

I should say about 5% of our patients had had X-ray treatment in experienced hands with apparently no benefit. Naturally we would get the unsuccessful cases, as operation is usually the last resort and our experience of this branch of treatment must be regarded in this light.

There is also this aspect of the question that treatment with X-rays very greatly increases the operative difficulty and danger. I know of at least two patients whose death under thyreoidectomy was due to previous treatment with X-rays.

Preliminary Surgical Treatment.

All focal sepsis must be cleared up; even though this may not be an ætiological factor, it improves the resistance of the patient and makes for a safer operation. Injections of boiling water and ligation of arteries is recommended and is valuable.

Surgical Treatment.

It is necessary to emphasize that this must be efficient and adequate. The failures after operation are generally due to the fact that sufficient thyreoid gland has not been removed. Thyreoidectomy is a most serious surgical procedure and the margin of safety in this operation is very small; the operation should be carefully planned and staged to suit the gravity of the case. It is an operation in which special skill is required, and the gland must be handled very gently. The shorter the operation, the safer it will be. Long operations under general anæsthetic in many cases often mean death. Anæsthesia plays a very great part in the safety of the operation; in fact it is probably the length of the general anæsthesia in a long operation that has such a bad effect. If ether anæsthesia is such a factor and a danger, then local anæsthesia should be and is the safest of all anæsthesias. As a matter of fact there is a small percentage of patients who will surely die under the most advantageous method of operation with ether and it is possible to save them with local anæsthesia. Operation under local anæsthesia requires a special technique.

In general anæsthesia Mott's dosimeter ether apparatus is used, but in most cases of exophthalmic goitre where the lobes are not very big and where tracheal obstruction would not be a factor, the lightest possible intra-pharyngeal insufflation only is used.

The method of operation is illustrated in a paper read before the Surgical Section and special attention is drawn to this method because it particularly lends itself to a method of staging which I consider is almost the greatest of all factors in making for safety in thyreoid operation. In bad cases the operation should always be staged. In my earlier cases I found that when I removed one lobe in one stage and allowed the patients to leave hospital, it was often difficult to induce them to have the second stage till the disease recurred, because they were quite satisfied with the very definite improvement. I have therefore adopted a method in which the second stage is done in ten days when, as Dr. Trumble has shown that among my patients there is a big drop in the basal metabolism and the disease has quietened down, the patient is very much better and the operation is only in continuation of the first one and is short and easy. Each stage can be done in about twenty to twenty-five minutes and, if the patient is very ill, the first may be done under local anæsthesia, but is usually done under light ether anæs-

thesia. The whole operation is therefore completed before the patient leaves hospital. In this method of operation if there is danger, it is possible to stop the operation at any moment and even with the ligation of the superior thyreoid artery.

In earlier years I held the opinion that the more thyreoid that was removed at one stage, the less was left to produce acute thyreoidism after the operation. I found by experience that the reverse was the case and that the patients with very severe symptoms who were operated on in stages, gave very little trouble with post-operative thyreoidism, compared with the patients who were not so ill and in whom the operation was completed in one stage. The amount of thyreoid which should be left depends on the type of case. In the small soft very vascular type with intense hyperplasia, as in the first group the tendency is to underestimate the intense toxicity of the small gland and leave too much. These are the patients who sometimes have three or four operations for recurrence and for a time are regarded as surgical failures, but they only need more thyreoid removed. With a large firm thyreoid and a fairly long history and mild hypertrophy and hyperplasia, the tendency is to take away too much and this is the reason why probably a few of our patients after operation manifest a drop in the basal metabolism.

Care of Exophthalmos in Certain Types of Exophthalmic Goitre.

In patients of the first group the exophthalmos may be most extreme and will require a great deal of management. Corneal ulceration may set in and panopthalmitis may follow, with loss of even both eyes. For example, one patient suffered from exophthalmic goitre for several years. She came into hospital suffering from acute exacerbations of the disease with all the characteristic symptoms. An immediate operation to save her sight was necessary and this was followed by an emergency thyreoidectomy. Dr. Edward Ryan's report is as follows:

> When Miss ———— came under my notice, both her eyes were proptosed practically on her cheek, the left eye being the more prominent. Nearly the whole of the cornea of each eye was abraded, except at the extreme upper portion, and the conjunctiva chemosed and dry like wax paper. I decided to operate on her at once by closing her lids. Under the anæsthetic (administered by Dr. Frank Davies) and very gently (for I feared the lenses would escape through the ulcerated surface) I attempted to replace the eyes behind the lids. I was unable to do so, but I freely divided both external canthi and was then able to return them into the orbit with a certain amount of difficulty. I then split both lids at the white line deeply and removed the lash bearing skin of the lower lid and inserted the bared wedge of the lower lid into the cleft of the upper lid. Then with mattress sutures in each lid and interrupted sutures in between I firmly closed the lids, except at the extreme portion of the inner canthus. All the sutures held and the lids were sealed. There was some mucus and purulent discharge for a few days, followed by a slight escape of tears from each day and next day the patient was fairly comfortable. I kept the right lid closed and gradually the proptosis diminished, until I felt I could safely open the right lid, which I did about one month ago (October). The cornea was quite opaque in its lower two-thirds, but there was an anterior chamber above and sufficiently clear cornea to provide for future irridectomy, which I think will enable her to have some vision in that eye. The left eye-lid is still closed.

Immediate Mortality.

Among three hundred patients with exophthalmic goitre there were three deaths. One death, of a patient in whose case I acted partly as an assistant and partly as an operator, is not included. Of these three deaths, two occurred among patients of the first group, both from acute thyreoidism, one in twenty-four hours and the other in three days. One death occurred in a patient of the second group and this was due to heart failure. The patient had had diphtheria about six months previously and the myocardium had apparently been damaged. These three deaths occurred in the group of sub-total thyreoidectomy done in one stage under ether, which comprises only about 25% of the sub-total thyreoidectomies done and would naturally include a rather better type of case than the other 75% in which the operation was "staged," because the patients were considered to be in a bad condition. In these there were no deaths; this shows how safe the very carefully "staged" operation was. There were no deaths among the patients on whom hemithyreoidectomy alone was performed. These three hundred cases would represent about four hundred and fifty operations on account of the "staging" methods used. It will thus be seen that the operation of thyreoidectomy carefully and conscientiously managed has a death rate very little greater than some of the operations which are considered much safer.

In order to ascertain the results of the operation, a comprehensive questionnaire was sent to two hundred patients chosen because they had been operated on many years. Short histories it was thought would not be of much value as an estimation of permanent cure on account of the exacerbations of the disease. One hundred and twenty replies were received and about half of these were personal reports. In those on whom an ideal sub-total thyreoidectomy had been done, as far as could be estimated, about 75% to 80% might be considered cured. About 10% to 15% would be considered partially cured and about 8% to 10% were not cured. In the last group there was apparently a re-growth of the thyreoid gland and a recrudescence of symptoms for this reason. One patient died three months after a sub-total thyreoidectomy with acute mental symptoms. Among the patients on whom hemi-thyreoidectomy had been done, there were 60% of cures, but these were individuals who had been specially chosen because their condition was eminently suited to this operation. They belonged to the third and fourth groups in which the thyreoids were partially burnt out or were toxic adenomas. There were 40% of failures, but this only meant that a second operation was necessary. Others failed to report, because the hemi-thyreoidectomy was only the first stage and were reported as failures or may possibly have been cured in other clinics. It is quite possible that these statistics are too optimistic, because the percentage was based on the replies received and it was quite impossible to trace all the patients to whom letters were written. Naturally the ones who were well, wrote and in some of the results sufficient time had not elapsed. But I trust they will serve as some guide as to the value

of the surgical cure in this meeting of physicians and surgeons.

What Place does Hemi-Thyreoidectomy Take in the Treatment of Exophthalmic Goitre?

As a routine it is a failure, but in carefully selected cases it is eminently satisfactory and even if it is risked in combination with medical treatment and the disease recurs in twelve months, the second lobe can be operated on. In this series it was done in the milder type of case and combined with medical treatment. Many of these patients are now quite well.

Some of my early patients subjected to hemi-thyreoidectomy and some of who were exceedingly ill and on whom the operation was performed nine or ten years ago, are quite well now.

It is interesting to note that these results go to show that an almost dramatic cure results from an adequate removal of the thyreoid gland in exophthalmic goitre, notwithstanding the fact that most modern evidence goes to show that the thyreoid is only secondary to some philogenetic influence acting through the sympathetic system.

THE TREATMENT OF EXOPHTHALMIC GOITRE FROM AN OPHTHALMOLOGICAL POINT OF VIEW.

By H. Riddell Stanley, M.B., B.S. (Melbourne),
Assistant Ophthalmic Surgeon, Victorian Eye and Ear Hospital, Melbourne.

In speaking on behalf of the Ophthalmological Section to-day I have deeply impressed in my mind the case of a patient with exophthalmic goitre who was under my care practically continuously from November, 1921, till May, 1922. It ended disastrously for both eyes, though the patient is in very good health at the present time, in fact physically better than she has been for some years.

Mrs. M., *aetatis* fifty-five years, was seen first by me in consultation on November 3, 1921, for lower marginal ulceration of both eyes, not responding to treatment and due to lagophthalmos (eyes closing to three millimetres).

Previous History.

Hemithyreoidectomy was performed in September, 1919, with temporary improvement in her general condition. She was seen by an oculist in February, 1920, and treated for corneal ulceration with good result temporarily. Her eyes remained fairly well till December, 1920; she was then seen by a general practitioner and treated for one month. They were apparently fairly well till May, 1921, when ulceration again occurred, which did not this time respond satisfactorily and I was consulted. After three weeks' treatment I advised her to become an in-patient of the Eye and Ear Hospital.

Condition on Admission.

The patient was pale and somewhat emaciated and very nervous. Her pulse rate varied between 100 and 110. There was no disease of the heart or kidneys. Moderate enlargement of the thyreoid gland chiefly on the side not operated on previously was present. Bilateral exophthalmos was noted; the eyes did not close within three millimetres. Fairly extensive lower marginal ulceration of both eyes was present.

The treatment adopted consisted of atropine, boric acid foments, boric acid and cocaine drops for pain only. The eyes were kept closed as much as possible. She was placed in a special darkened ward.

Chemosis developed on December 15, 1921, with some purulent discharge. "Argyrol" (10%) was ordered to be used thrice daily.

On December 23, 1921, severe pain came on in both eyes. "Aspirin" and bromide of potash were given, leeches were applied and atropine changed for scopolamine on account of possible atropine irritation.

On January 6 corneal ulcers were steadily increasin in size and the eyes were becoming very irritable and painful. Atropine was re-ordered and "Argyrol" reduced to 5%.

On January 27, 1922, there was very severe pain. Morphine and "Veronal" were given.

On January 28, 1922, practically complete thyreoidectomy was performed under ether. Recovery from the operation was uneventful.

On February 13, 1922, the ulceration seemed to be temporarily checked.

On February 15, she wore a bandage at night only and "Argyrol" (10%), atropine (0.5%), cyanide of mercury lotion (1 in 5,000), and yellow oxide of mercury ointment at night were employed.

On March 7, 1922, conjunctival swabs were taken. *Staphylococcus aureus* was isolated from the right eye and *Staphylococcus albus* from the left eye. Vaccine treatment was started on March 22, 1922, and continued till April 8 with no definite result. The ulceration was then affecting half of the right and two-thirds of the corneæ and was rapidly increasing. Atropine was reduced to 0.25%. Very severe pain was constantly complained of.

On April 29, 1922, the left cornea was perforated. Excision of the eye was carried out on May 2, 1922. The right cornea became perforated a few days later and this eye was also removed. The patient was discharged from hospital on May 27, 1922.

The intense chemosis of lids which was so prominent a feature of the case disappeared shortly after excision of eyes.

All the other general features of the disease cleared up within a few weeks of the complete thyreoidectomy, but the exophthalmos was only slightly reduced. This seems to favour the theory that the exophthalmos is at first congestive and muscular in origin, but that later on there is definite increase in the orbital tissue. If this be so, it seems to indicate that early surgical interference of a most thorough nature is the best means of dealing with the exophthalmos, unless it can be definitely shown that medical treatment (gland extract or drugs) or radio-therapy can produce similar or better results. Failing this it would seem that these methods should be used only where operation is contra-indicated or when the patient is strongly averse to surgical treatment.

In any case local symptomatic treatment wastes valuable time and gives a false sense of security. In any future case of this kind I should certainly advise early complete thyreoidectomy.

THE TREATMENT OF EXOPHTHALMIC GOITRE.

By H. Hume Turnbull, M.D. B.S. (Melbourne).
Honorary Physician to Out-Patients, Melbourne Hospital.

Discussion as the proper treatment of exophthalmic goitre is still being actively carried on, which suggests that so far a really satisfactory method has not been evolved; but there are now few who uphold general medical methods as opposed to X-ray or surgical treatment. Correct figures of the results of medical treatment are not readily obtained, but Hector Mackenzie gives 25% as the mortality, while Campbell's figures show 15% of deaths and 17% not improved.

In Hale White's series most of the patients seem to have gained little from their stay in hospital, though many recovered gradually after discharge.

The prospect of a crippled survival after years of chronic ill health, which the last observer's figures hold out, is a dreadful one. With a few exceptions in special rare cases medical treatment may be expressed as rest, bromide and quinine in some form, as there is no evidence to support the claims of any of the various special treatments. There can be no doubt that some patients do get quite well under such treatment; probably all of us have seen such results, but relapses are not unknown, a very long time is necessary, far more than can be spared by those whose living depends on their own exertions, and the result is very often most unsatisfactory.

The so-called medical cures nowadays do not seem to be more striking than the not infrequent remissions and recoveries without treatment. Reported results from X-ray treatment are much better than those got by medical treatment without irradiation, but it seems that judgement as to the value of this form of treatment must be suspended till more consistent results are shown.

Means who has reported many cures, also admits many failures and he is quite definite in placing a time limit, now four months, on this treatment. If there is no definite result in that time, he advises operation and his reported cases show that remarkable improvement occurred after operation in patients in whom X-ray treatment failed.

In any consideration of operation results early figures must be omitted. Many deaths then were due to the use of chloroform, an anæsthetic so dangerous in these cases as to be absolutely unjustifiable, and the only interest of such cases is the realization that medical results must have been bad indeed to allow surgery to win any place under such an immense handicap.

Now many patients are successfully operated on who only a few years ago would have been considered far too ill for any such procedure; and modern surgical figures include many extremely bad cases.

It is necessary to insist that operation must be complete; the treatment should not be classed as a failure because an incomplete removal is not satisfactory.

On the other hand special skill and experience are required for satisfactory results in this surgery and many bad results are almost certainly avoidable.

My own experience of X-ray treatment is not large, but it has not encouraged me to perservere very long. I have not seen any result comparable to a good surgical result and the best results I have seen have been in cases in which a partial thyreoidectomy has given much relief, but symptoms have recurred to some extent. In several such cases X-ray treatment has helped materially and by its use further operation has been avoided.

It seems to be fair to state that the only generally accepted treatment for the condition is operation which is becoming more and more frequent, and as the conditions for and the technique of the procedure are clarified, the results are progressively improving.

The condition should not be regarded as a surgical emergency. The only possible exception to this rule is in cases where the exophthalmos is so extreme that there is real danger of the destruction of one or both eyes. Here it may be necessary to operate at once to endeavour to save them, but the result is frequently unsatisfactory, though the operation may in other respects be a success.

In all other conditions it is well to allow a period for medical treatment, preferably combined with X-ray treatment.

In patients in whom gastro-intestinal symptoms are prominent, the risk of operation is considerable, while, except in hopeless cases, sufficient improvement usually follows rest to allow of operation during a period of diminished toxæmia.

Most authorities are agreed as to the occurrence of remissions and exacerbations in all cases. As a rapid fatal ending is exceedingly rare, it is safe to wait for a remission, during which operation may be performed.

No cardiac condition will of itself contra-indicate operation, although, of course, there will come a time in a neglected patient when any interference is obviously too late.

Mere rapidity of the heart's action can be accepted as an index of the thyreoid toxæmia and rest will practically always result in improvement. Such rest should certainly be given and continued if necessary for some weeks before operation is attempted.

When auricular flutter or auricular fibrillation occurs, it is a strong hint that milder measures should be abandoned and operation performed, as such conditions, though sometimes of short duration at first, tend to recur and finally to become permanent.

Auricular fibrillation in exophthalmic goitre almost always results in a rapid ventricular rate and this with a poisoned ventricular muscle soon brings about failure.

There is still room for doubt whether these conditions should be regarded as indicating actual muscle damage or not, but evidence is accumulating in favour of the view that in a heart whose muscle is normal, but poisoned by a toxin, auricular fibrillation may readily occur.

The actual impulse which starts such fibrillation, is unknown, but is probably nervous and from the sympathetic; we know that in poisoned hearts this type of arrhythmia may occur on stimulation of the accelerator nerves.

If this be true and the heart muscle be at first not actually damaged structurally, it is reasonable to assume that if toxæmia be abolished and the normal rhythm restored, the heart will be normal again.

This result has been obtained by several observers and will probably be much more common as experience increases.

Restoration of the normal rhythm may follow the use of quinidine, even in exophthalmic goitre, but if the thyreoid intoxication is still actively present, a recurrence of fibrillation is practically certain to take place.

In such cases the treatment is very trying to the patient, as the increased ventricular rate preceding the restoration of normal rhythm causes most unpleasant bumping.

After a successful operation there is a tendency for the normal rhythm to return quite apart from special treatment. I saw two patients under the care of Dunhill in whom auricular fibrillation, present before operation and still evident three weeks later, had disappeared when the patient returned after three months.

This happy result is by no means universal, but now we have in quinidine a drug which will restore normal rhythm in 60% to 75% of patients. If the thyreoid intoxication is previously removed by efficient and sufficient operation, there is little doubt that normal circulatory conditions will be restored to many more patients, which means very greatly increased comfort as compared with even a controlled fibrillation. Experience has shown that in patients suffering from exophthalmic goitre the heart with auricular fibrillation will respond to digitalis very satisfactorily and therefore digitalis should always be pushed in such cases and an efficient circulation restored.

In a patient with a rapid irregular heart, anarsarca and grave dyspnœa operation should never be undertaken till the condition has been controlled by medical treatment.

This cannot be too strongly urged, as success in such cases is often claimed as a surgical triumph, instead of the error of judgement it undoubtedly is.

Full doses of digitalis, aided in some cases by the occasional use of diuretics and by necessary sedatives, will reduce the ventricular rate to eighty or below and the cardiac distress disappears.

The patient should be allowed a week or two of circulatory comfort before operation, to allow the overtaxed ventricular muscle to be properly rested, oxygenated and cleared of its accumulated metabolic impurities and to allow the bronchial and pulmonary congestion to resolve.

It will be found that these patients will then take ether as well as any others and give no special worry to surgeon or anæsthetist, whereas without such treatment they are notoriously worrying.

The preliminary dose of atropine given before operation usually results in a ventricular rate of one hundred and ten to one hundred and thirty with unpleasant throbbing, but the rate settles down again in about half an hour and there is no heart failure as a result.

After operation digitalis in moderate doses should be kept up for a week or two and then, when the toxæmia has disappeared or is greatly diminished, quinidine may be given.

If there has been a long period of failure or the heart has been much weakened, it seems wiser to continue digitalis for several weeks and to allow the patient to regain some strength and confidence and then to put her back to bed and exhibit quinidine.

A satisfactory result can be looked for with some confidence if sufficient thyreoid has been removed; in such cases there seems little chance of return to a state of fibrillation unless the thyreoid toxæmia recurs.

If fibrillation returns and there are signs of thyreoid intoxication, it is probably futile to use quinidine again, but digitalis should be persisted in in sufficient dose to keep the ventricular rate within bounds and later on further operation will usually reduce the toxæmia to a level at which the normal rhythm will persist when restored by quinidine.

To sum up I should advise a patient with exophthalmic goitre who is anxious to avoid operation and to whom time and money are no object, to submit to some months complete rest with bromide, quinine, and X-ray treatment. If the result is then not really satisfactory, that is, if in six months there is not restoration to a good economic level with slow pulse, adequate circulation and absence of tremor, I should urge thyreoidectomy with removal of one lobe and the isthmus at the first operation. The patient or at least her friends should realize that further operation may be necessary, though no more should be done at first. If this is not made clear, they may go away with the idea that surgery has failed.

I frequently see patients in whom only one lobe has been removed, and who regard surgery as a failure because they are not cured, though it is very doubtful if so small an operative removal will cure any patient with severe signs.

If heart failure with or without auricular fibrillation be present, it should be treated as indicated, but it should be regarded as a definite indication for early, though not urgent operation.

If this be done, I feel sure that many hearts now regarded as severely crippled will be found to return to a nearly normal function; but long delay in such cases means progressive and later irrecoverable degeneration.

If the case is severe or becoming rapidly worse or if there is any suggestion of damage to other organs, operation is advisable; and many patients prefer it to the prolonged rest otherwise necessary, but it is reasonable to make an attempt to avoid it if possible.

In hospital practice or when the economic factor enters appreciably, I should always recommend operation as the treatment after a short period of rest.

Between operation and exposure to X-rays, as the only forms of treatment of accepted value, the former seems to have more successes, fewer failures and does not appear to be followed by myxœdema to anything like the same extent.

I feel sure that one of the chief handicaps to success with this disease is the want of any standard method of treatment, so that patients drift about from one doctor to another and waste valuable time through no fault but their own.

I have seen some good follow the removal of septic teeth, tonsils *et cetera*, but have yet to see such treatment cure a patient.

Dr. J. F. Chambers said that a discussion on exophthalmic goitre would perhaps be incomplete without some reference to basal metabolism and he would confine his remarks to a summary of its position in regard to clinical application.

The method which he believed best combined convenience with accuracy, was that in which a combination of the Douglas bag and Haldane gas analysis apparatus was used. The patient's caloric production was determined through the respiratory exchange over a given period and was expressed finally as a percentage of the normal calorie production for an individual of the same age, sex, height and weight. In the same sense that a pulse rate of from 60 to 80 per minute might be taken as constituting the normal, a basal metabolic rate of from—10% to + 10% of the standard might be regarded as normal. Slight daily, seasonal, climatic and other variations occurred in the basal metabolic output, but these were of little consequence as compared with the extent of variation met with in abnormal thyreoid conditions. This depended, of course, upon the property of thyroxin which increased the metabolic processes when it was present in excess; when thyroxin was present in subnormal amount, the metabolic

activity was correspondingly diminished. In gross myxœdema metabolic rates below 40% might be registered, while in severe hyperthyreoidism 100% might be recorded.

It was true that so far as diagnosis was concerned, estimation of the basal metabolic rate was seldom required in such well defined conditions and in the doubtful cases, while the result was sometimes practically conclusive, at other times border-line readings failed to dispel the doubt.

The application of basal metabolism to exophthalmic goitre was in the main two-fold: (i.) for diagnosis and (ii.) as a control in treatment. Before utilizing estimations of the basal metabolic rate as a means of diagnosis, it was necessary to recognize and exclude all other conditions which definitely affected the metabolic rate. This was probably not difficult to do.

The rate was raised by (i.) any condition which entailed physical or respiratory distress on the part of the patient or in other words prevented the assumption of the basal state. It had been shown experimentally that to attain the "basal state" required at least twelve hours abstinence from food and twenty minutes absolute rest in bed. It was also raised by (ii.) the presence of fever, (iii.) tissue breakdown consequent upon the "primary" blood diseases (pernicious anæmia and leuchæmia) and (iv.) active acromegaly.

The rate tended to be lowered by (i.) thyreoid deficiency, (ii.) starvation, (iii.) severe asthenia (as in Addison's disease) and (iv.) pituitary deficiency particularly of the Fröhlich and Cushing types.

In diabetes the disordered metabolism gave results which appeared very erratic and difficult to interpret.

When thyreoid derangement was suspected, the assistance provided by estimations of the basal metabolic rate might in the first place denote what type and degree of secretory abnormality, if any, existed and in the second place might separate hyperthyreoidism so called from the conditions which simulated it. The latter were usually some variety of those psychic and nervous states collectively referred to as the neuroses and less often early infections, such as pulmonary tuberculosis, in which loss of weight and strength, transitory fever, tachycardia and sweating might lead to suspicion being cast upon the thyreoid gland.

In the control of exophthalmic goitre a series of metabolic estimations made under the same conditions at weekly or greater intervals in his experience constituted the most effective single measure for observing the progress of the patient and computing the value of treatment whether it were medical, surgical or radiological. It was difficult to see, however, how estimations of basal metabolism could ever be widely employed in practice. There were already sufficient extraneous sources of error in the procedure and they could not afford to add to these by the employment of other than the most accurate methods. This implied initial expense and apparatus which demanded considerable care and attention. The process itself was most time-consuming, requiring on the average two to the three hours at all events before the first satisfactory reading was obtained. Finally it was probably many weeks or months before the practitioner became sufficiently familiar with all aspects to obtain reliable results.

Dr. G. N. Lorimer said that during the last few months he had examined thirty-six patients with exophthalmic goitre upon whom Mr. Devine had operated. The average length of time since operation was three years. The object was to estimate the basal metabolic rate and to compare this with any symptoms present and to correlate both to ascertain if the surgical treatment undergone had resulted in a cure. The results taken as a whole showed that the metabolic rate was within the normal range except in seven patients. Of these four showed an increase and three a decrease, although in no instance was this very far removed from the normal.

He had grouped the patients into age periods of ten years. In the first group aged from twenty to thirty years, there were thirteen and with two exceptions, these were all young unmarried women. Therefore this group could be called the young unmarried woman group. This provided the most acute forms of disease. Eight of this number could be dismissed at once. They were free from all symptoms and had a normal basal metabolic rate. Each played tennis, danced and did all the things that a normal young woman did. One was a male; he played football and had since married.

In addition to the brilliant surgical technique, the good result was to a great extent dependent on whether the patient could be placed under favourable living conditions. Each of the patients lived with her relatives and the home surroundings were such that complete and prolonged mental and physical rest could be undertaken. The opposite condition was illustrated in the case of a young woman of the domestic servant class. This young woman had had three operations in 1919, 1920 and 1921. However much rest had been taken, she was not immune from the mental and financial worry of a forced inactivity. She had the advantage of the same surgical skill as the others, but her thyreo-toxicosis only had been relieved after the third operation. The only patient in this group who had an increased metabolic rate, was a young married women. She had had a partial operation in 1918 and had not returned to complete the treatment. She had been well till seven months previously, when she had begun to develope some of the symptoms of thyreo-toxicosis.

There was another type of case in the group in which the symptoms had been present for many years and in which there was a sudden acute exacerbation.

These cases were a great anxiety, but successful surgical treatment was almost dramatic. He instanced the case of a young woman who had had exophthalmos and hyperthyreoidism for a number of years. After some great mental anxiety an acute condition had developed in which her bulging eyes almost left her head, with trembling so severe that it shook the bed from which she was unable to move. Six months after operation she was employed in a military hospital helping to cook for one hundred men and except for a considerable degree of exophthalmos and a large heart, she shows no sign of her former condition. In a similar case, the exophthalmos was so extreme that eyelids had to be sutured to prevent dislocation. She had been operated on and her basal metabolic rate had been reduced to within normal limits.

The age period of from thirty to forty years might be called the young married woman group. In this group there were eight patients and except for one the metabolism was within normal limits. The exception was aged thirty-eight and had had two operations in 1920 and 1921. Her exacerbations seemed to be connected with pregnancy.

He thought that if more patients had been examined in this group, a larger proportion would have been found in whom the condition was not totally relieved. It would be expected that any tendency to hyperthyreoidism would be exaggerated in such women with the numerous anxieties of home and children. Of the eight patients examined, two were unmarried, so it was not a very representative series.

In the third group of patients between the ages of forty and fifty there were thirteen. Two showed an in-

creased rate and one of these had since undergone further operation. The other had had a partial operation in 1917. She manifested some degree of thyreo-toxicosis.

There were two patients over fifty and in these a metabolic rate was within the normal limits. Both were women with considerable exophthalmos.

In the whole series he found that three people had a basal metabolic rate below the normal; apart from a rather rapid increase of body weight, they showed no signs of myxœdema. Nothing further was noted to suggest that the amount of gland left was insufficient.

THE FRACTIONAL TEST MEAL AND ITS VALUE IN RESEARCH, DIAGNOSIS, AND TREATMENT.

By FRANK L. APPERLY, M.A., M.D. (Oxon), M.R.C.S. (Eng.)
Acting-Professor of Pathology, University of Melbourne.

THE basis of the method can be expressed in a formula which depends on certain phenomena taking place in the stomach. These phenomena are:

(1) The secretion of acid gastric juice, (2) the emptying of stomach contents into the duodenum and jejunum, (3) the regurgitation of duodenal alkaline fluids into the stomach.

This regurgitation of duodenal fluids is a phenomenon of very great importance in gastric work and its investigation here and elsewhere has yielded information about the pathology of function in different dyspepsias which enables us to explain much that was previously unknown. Now the acidity or strength of acid of the gastric contents at any one moment equals

$$\frac{\text{Total active HCl in the stomach.}}{\text{Total volume of gastric contents.}}$$

The total active hydrochloric acid in the stomach is the resultant of the total hydrochloric acid secreted less the total hydrochloric acid lost in the chyme and the total hydrochloric acid neutralized by alkali, while the total volume of gastric contents at the same moment will be the sum of the volumes of the test meal introduced, the gastric juice secreted, the regurgitated duodenal fluids, less the volume of the chyme lost.

This formula gives us the basis for many mathematical deductions and without going into detail it is easy to prove that the acidity can be raised by (a) increasing the rate of emptying, (b) decreasing the rate of alkali reflux and (c) increasing the rate of secretion of the gastric juice.

Any of these factors acting alone can raise the acidity level far above the normal and produce hyperchlorhydria by which, we mean, not an increased strength of hydrochloric acid in the secreted gastric juice (for this never occurs), but an increased percentage of gastric juice in the food or a diminution of the normal rate of neutralization by regurgitated duodenal alkalis.

Of these three factors the secretion of gastric juice varies probably very little (except in cases of actual destruction of gastric mucosa and in certain cases of inborn defect), much less than might be thought. Excepting these cases when rate of secretion is decreased (as in cancer, pernicious anæmia, and others) we are left with only two factors: (i.) The varying rate of stomach evacuation determined by gastric movement and (ii.) the varying rate of reflux of duodenal alkali determined by duodeno-jejunal activity.

In brief then, our formula and therefore variations in acidity depend first and foremost on movement and variations in the curve of acidity made by plotting the acidity at different intervals are the result of movement and not of secretion. This is the essential point to realize. From the curve obtained we can deduce the various gastro-intestinal movements and in so far as these are characteristic of certain lesions and certain diatheses, so diagnosis of these is assisted.*

Variations from the Normal Form of the Acid Curve, and Their Value in Diagnosis.

Although increased secretion probably occurs in certain diseases, the effect is of little importance compared with other influences and we need not consider this any further. Diminution of secretion will be dealt with later.

The second factor, however, the rate of emptying, has a very considerable influence in determining the rate of rise of acidity. In Figure I. shown, the curve N has been constructed from average normal figures. Curves B2, B3 and B4 show the comparatively small effect of doubling, trebling and quadrupling the secretion, while the curves C2 and C3 show the effect of doubling and trebling the rate of gastric evacuation. The relative effects of these factors is obvious.

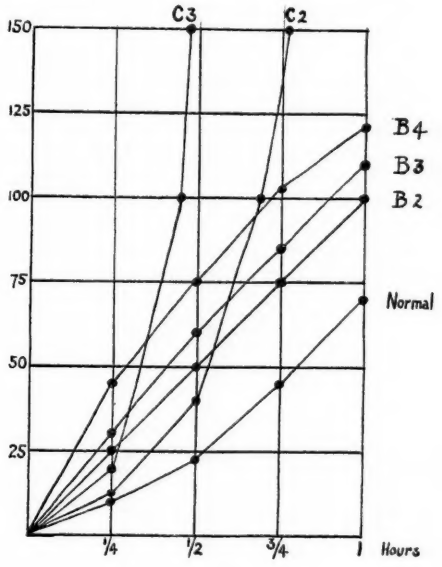

FIGURE I.

The chief type of case in which rapid evacuation, at any rate at the beginning of the test, is seen, is in duodenal

* The technique, an explanation of the normal form of the acidity graph, a summary of the advantages of the method and some observations by the writer were here discussed.

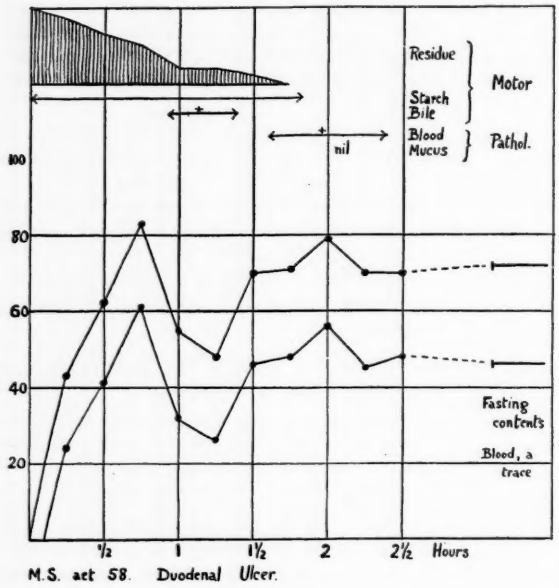

FIGURE II.

ulcer. There is not only a quickened evacuation, often with gastric hypertonicity, but for the same reasons little or no alkaline reflux. The result is that the acidity not only rises rapidly, but reaches a high level in the typical cases. Often some pyloro-spasm occurs later, maintaining the exclusion of alkali and therefore maintaining a high plateau curve. It is this rapid rise with maintained plateau and high termination that is so typical of duodenal ulcer. High rise alone can be caused by several conditions of rapid emptying reflexly produced, but the plateau showing pyloro-spasm strongly suggests ulcer. Note in this case that a full diagnosis can sometimes be made by the appearance of blood simultaneously with bile or a drop in the curve (see Figure II.).

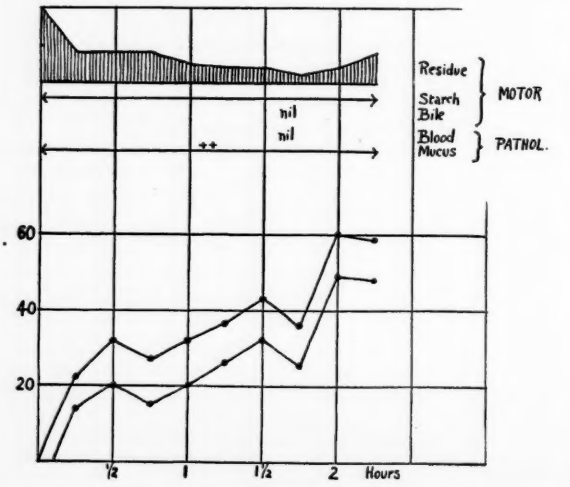

FIGURE III.

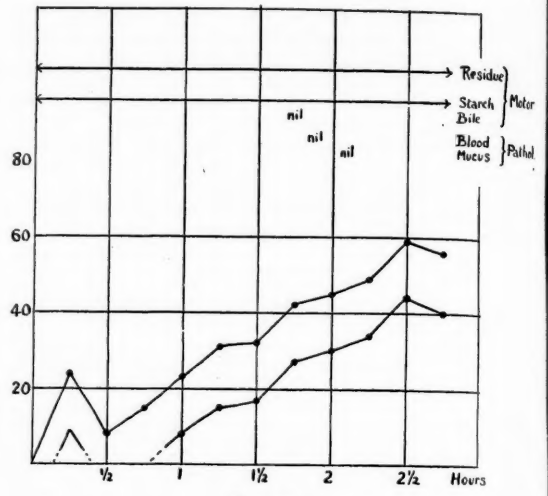

FIGURE IV.

In the extreme opposite condition, where gastric evacuation is reduced to nil, *id est* there is pyloric obstruction, there must obviously also be a cessation of alkaline reflux. The continued secretion, therefore, raises the acidity at a fairly uniform rate, as shown in Figures III. and IV., one a case of greatly dilated stomach, the other a case of *tabes dorsalis* with gastric crises.

Sometimes very much the same chart is given by pancreatic disease and in a number of these cases now we have been able to return a correct diagnosis. Owing to the lack of pancreatic alkali the acid curve goes on steadily rising. Obstruction as a cause is ruled out by the presence of bile in greater or less quantity after an hour or so, *id est* the duodenal juices can reach the stomach, but in spite of this no neutralization occurs. The condition of the patient shown was diagnosed in the ward as duodenal ulcer, but operation revealed a large pancreas with fat necrosis in the omentum (see Figure V.). When

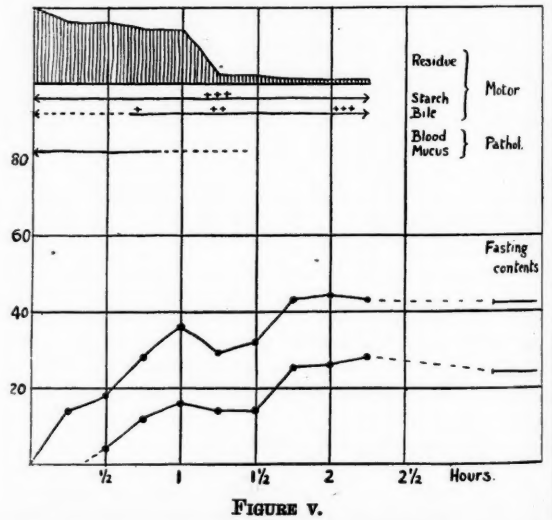

FIGURE V.

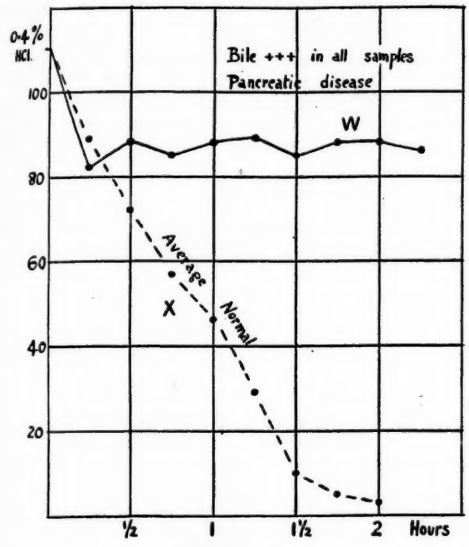

FIGURE VI.

two hundred and fifty cubic centimetres of 0.4% hydrochloric acid was introduced through the tube into this patient's stomach, he failed to neutralize it, whereas normally acidity falls to zero in little over one hour (see Figure VI.). Yet all specimens were strongly bile-stained. Other observations tend to show, however, that when the pancreatic insufficiency is long maintained, the chart is of quite a different type. This will be discussed later.

Variation in the amount of duodenal reflux is by far the most important influence affecting gastric acidity. Recent work in Melbourne, published and unpublished, shows that this depends on variations in jejunal activity. Many cases of absence of free hydrochloric acid are really due to complete neutralization of a normal amount of secreted gastric acid and all the evidence goes to show that the jejunum is at fault, an undue irritability being present. Hence in many cases of intestinal upset we find this absence of free hydrochloric acid. Of course, there is the opposite relationship where non-secretion of hydrochloric acid leads to a gastro-genic diarrhœa and to intestinal infection. In these cases the rate of stomach emptying is generally rapid, whereas in the former obviously the rate of evacuation is slowed. Another point about these latter cases is that the lack of hydrochloric acid secretion is often inborn. One healthy student examined last year had no free hydrochloric acid and a very low total chloride. Knowing that acidity curve types tend to run in families, we asked if any of his blood relatives had ever suffered from any of those diseases which so often accompany achylia. He replied: "My father died last year of pernicious anæmia."

While on this point of family type I might give you another instance. Figures VII. and VIII. show the test-meal charts of a mother and her son. The former has suffered for some years from duodenal ulcer (clinical diagnosis); the latter is quite healthy, but gets slight hunger

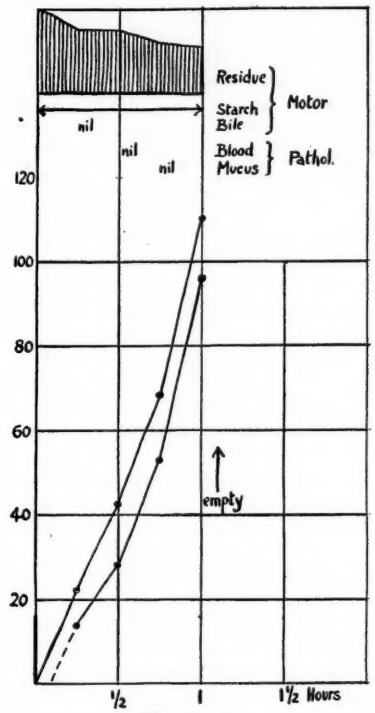

FIGURE VII.

pains when overworked or run down. To return to these cases of overactivity of the jejunum, we find it associated with some types of appendicitis, where the appendical

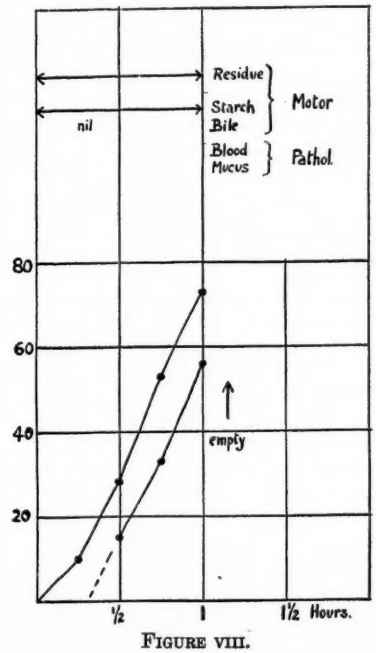

FIGURE VIII.

lesion is either the result of an intestinal infection, as suggested by Hurst, or the intestinal irritability is due to the appendicitis; also in many gall-bladder and chronic pancreatic conditions, in which, according to Cammidge, the lack of pancreatic alkali may produce an alteration in the intestinal flora with the presence of abnormal products of bacterial activity. These products are highly irritable and are probably the cause of the over-activity of the jejunum, with consequent neutralization of free acid.

On the other hand, in some conditions the jejunal activity is lower than normal or the activity of the duodenum and upper part of the jejunum is too great to permit of intestinal reflux. In these cases of which duodenal ulcer is again the typical example, we have besides an abnormally rapidly emptying stomach an inability of the alkaline juices to reach the upper region of the duodenum, with the result that not only does the gastric acid remain high, but during fasting unneutralized acid remains in the duodenal cap, producing pyloric spasm and pain. This explanation is supported by the fact that gastro-enterostomy for duodenal ulcer is in the majority of these cases not followed by any neutralization of gastric acid at all, so that the acidity chart remains the same in value and form as before operation. The stomach and its stoma are above the reach of the jejunal reflux forces. We have some unpublished evidence that the rôle of gastro-enterostomy is to augment these defective upward reflux forces of the jejunum by the expulsive force of the stomach. After this operation by which the stomach is made to empty into the intestine below the point of entry of pancreatic juices, the expulsion of gastric contents causes part of these contents to ascend the duodenum, carrying alkali before it, with neutralization of acid in the duodenal cap and removal of the cause of pyloric spasm and pain.

Coming now to the question of treatment, we find the method of more real value. We know that gastro-intestinal symptoms, as a rule if not always, are of motor origin and the fractional method is chiefly a record of motor activities. Consequently if the record shows over-activity of the jejunum with consequent neutralization of all gastric acid, we should direct our treatment towards removing the cause of and damping these activities. Again in duodenal ulcer and other conditions giving similar symptoms, medical treatment should in addition to the usual methods attempt to stimulate jejunal activity and lower duodenal irritability and tone. The use of olive oil is a good example of this effect. I am not in a position to say much about this at present, because our experience of methods framed on these lines goes back for only a short time, but so far our results have been most encouraging. Let me discuss only one type as an example. It has long been the custom to treat absence of free hydrochloric acid in the stomach by giving dilute hydrochloric acid and undoubtedly this is the correct treatment in those cases, a minority in which secretion is absent or diminished. But in the cases in which the condition is due to over-neutralization, the most rational way is to depress intestinal activity. I have found that hydrochloric acid in these patients often frankly is not tolerated and in others it relieves symptoms, but is accompanied by distressing flatulence. Treatment framed on the lines indicated has so far been much more successful than the hydrochloric acid treatment, but more experience is required before definite statements can be made.

One value of this method has already been suggested: the effect of the personal factor in each case. Each person has his own type of acidity chart, that is his own type of gastric and intestinal movements. Consequently a lesion will probably have more effect in producing symptoms in one person than another. This method shows the final result of personal factor *plus* that due to the lesion and it is this combination which we must treat. The method shows this combination and therefore suggests the treatment.*

Professor Carmalt Jones referred to the work of various observers as to the variations that occurred in the results of fractional analyses of the stomach contents of people who were apparently normal. For example Ryle had found great variation in the acidity and rapidity of emptying the stomach of people without symptoms. Dr. Apperly's views that the variations were dependent on gastric activity were not those held by Hurst and Ryle. Hurst believed that people with rapidly emptying stomachs were prone to duodenal ulceration. Professor Carmalt Jones believed as a result of his experience that patients with duodenal ulcer yielded a high resting acidity, a rapidly declining curve and rapid emptying within two hours. He emphasized the fact that in patients who exhibited all the evidence of gastric or duodenal ulcer the signs and symptoms might be dependent on chronic appendicitis.

Dr. C. B. Blackburn agreed with Dr. Apperly's views. He thought that the nature of the meal given to a patient made a great difference to his symptoms. One who had hunger pain and other symptoms of hyperchlorhydria on a meat diet, might be quite free from pain and so on on a mild or gruel diet.

In his reply Dr. Apperly pointed out to Professor Carmalt Jones that movement was the central factor in acidity and its variations, provided that the gastric mucosa was healthy and that achylia of congenital origin was not present. Even when the quantity of secretion was doubled or trebled, it made small difference to the acidity as compared with increased rate of emptying or decreased neutralization with duodenal alkalis. The plateau of acidity following the sharp rise often seen with duodenal ulcer was not confined to that lesion. It merely indicated a failure of the duodenal fluids to enter the stomach, generally the result of pyloro-spasm. This pyloro-spasm might be the result of duodenal ulcer, but it might also be caused by appendicitis or other reflex conditions. Hence the type of curve "typical of duodenal ulcer" might also occur in reflex conditions.

Dr. Apperly said that, though the gruel of the test meal might not and generally did not elicit the symptoms that other foods elicited, it did reveal gastro-intestinal tendencies which would give the cue to those activities most likely to be affected when the adequate stimulus supplied by ordinary food was present. The difference between the emptying time determined by X-ray and fractional test meal examinations to which he had referred at the end of his paper, indicated that in some instances the barium probably stimulated a spasm, while gruel did not do so. In such circumstances the cause of a pain symptom might be missed, as suggested by Dr. Blackburn.

* The reasons for differences in the emptying time as shown by this method and by X-ray examination were here discussed, with their significance and value.

EPIDEMIC ENCEPHALITIS.*

By J. B. CLELAND, M.D., CH.M. (Sydney),
Professor of Pathology, University of Adelaide.

The contributions of the Pathology Section to this discussion on epidemic encephalitis may be classified under the following headings: (i.) What forms of epidemic encephalitis in man exist and which of these have been recognized in Australia? (ii.) What pathological changes are met with, are such pathognomonic for each form, do these changes explain the clinical symptoms and what significance can be attached to their presence? (iii.) How in each form is infection conveyed from one person to another? (iv.) Is there any evidence of immunity being established?

The Forms of Epidemic Encephalitis.

There are two universally admitted forms or species of epidemic encephalitis due unquestionably to distinct specific viruses, namely acute polio-encephalo-myelitis (the old infantile paralysis) and *encephalitis lethargica*. In some epidemics of the former medullary or encephalitic localization may be a prominent feature in the cases. The latter is usually encephalitic. I have for some time held that hydrophobia and mumps probably also belong to the same group of viruses, as outliers or aberrant members. It has recently been shown that in febrile herpes a virus is present capable of giving rise to acute encephalitis in rabbits. Some writers hold that this virus is probably the same as that of *encephalitis lethargica*, others that it is distinct, a proof of its separate nature being seen in the fact that patients who have recovered from lethargic encephalitis, may still react when the herpetic virus is applied to the skin (that is they have not acquired immunity to the herpetic virus). *Herpes zoster* seems due to another separate virus. Recently the French school have tacked on variola and varicella to the group. They consider that this group includes viruses capable of attacking epiblastic tissues and of giving rise to a marked immunity. Some members, such as small-pox and chicken-pox, attack chiefly or almost entirely the skin epiblast, others, such as the viruses of encephalitis, the epiblastic central nervous system.

We have therefore several divisions in the group. Thus: Skin ectodermoses—variola, chicken-pox, foot and mouth disease (?).

Ectodermoses affecting the skin and sometimes the central nervous system,—herpes zoster, febrile herpes.

Ectodermatoses affecting the salivary glands and rarely the central nervous system—mumps.

Ectodermosis affecting the central nervous system and probably the salivary glands (saliva infective)—hydrophobia.

Ectodermoses affecting the central nervous system—acute polio-encephalo-myelitis, *encephalitis lethargica*.

The two last diseases concern us this afternoon. The former has long been known in Australia. Sporadic cases are common and mild epidemics have occurred and been reported. I have given a history of the disease in Australia up to 1913 in the fourth report of the Microbiological Laboratory Government Bureau of Microbiology, New South Wales, for that year (page 262). Medullary and encephalitic cases have occurred in the outbreaks, though most cases have been spinal. Campbell, Bradley and I in 1918 (THE MEDICAL JOURNAL OF AUSTRALIA, February 16, 1918, page 123) reported the successful transmission of the virus to a monkey.

A number of cases conforming to *encephalitis lethargica* have been reported, chiefly in Victoria, since this disease was recognized a few years ago.

The Australian form of encephalitis to which we applied the term "X-disease" requires full consideration. The term "X-disease," to which some objection has been taken, was employed because we were undecided as to whether the complaint was merely the encephalitic form of ordinary polio-encephalo-myelitis or a distinct entity. This doubt still exists. Another possibility is that the disease was really *encephalitis lethargica*. Material from cases and from laboratory animals was submitted to Simon Flexner in America and in communicating with me he stated that the histological picture was not that of *encephalitis lethargica*, but did correspond with that of ordinary acute polio-encephalo-myelitis. The points on which stress may be laid in the differentiation of the two conditions, are the following: In both perivenous sheaths of rounded cells occur. Cellular islands may also be present. Neuronophagocytosis is not a prominent feature in *encephalitis lethargica*, but is so in the other disease. In acute polio-encephalo-myelitis the meninges may be involved and associated with the rounded cells in the various situations polymorpho-nuclear leucocytes are apt to be present, the converses of these holding in *encephalitis lethargica*. *Encephalitis lethargica* tends to involve the brain cortex, basal ganglia, pons and medulla, thus accounting for the prominence of ocular symptoms and the lethargy. The other disease attacks more particularly the spinal cord, involving in some cases in an epidemic the medulla and occasionally affecting the brain cortex, basal ganglia, pons and medulla alone or in addition to the spinal cord. In some outbreaks an undue number of encephalitic cases occur.

Another means of differentiation is by means of animal inoculation. The Australian "X-disease" agrees with acute polio-encephalo-myelitis in being transmissible to monkeys as our experimental results in Sydney showed conclusively. The virus of *encephalitis lethargica* does not seem to be thus directly transmissible to monkeys, but can produce encephalitis in rabbits and it is said that after such passage it may then be transmitted to monkeys. On histological grounds and on the results of animal inoculations it would seem that the Australian disease is not *encephalitis lethargica* and is therefore either the encephalitic form of acute polio-encephalo-myelitis or a separate entity.

Flexner in correspondence with me says he is loath to admit the occurrence of another disease of this group, but is puzzled over our conveyance of the Australian type to sheep, a calf and a foal. He raises the possibility of the accidental association with the original virus during the animal inoculations of some other virus capable of giving rise to the results obtained. It would seem that this virus, if present, was not an ordinary bacterial one.

*This paper was read after Dr. Marshall Macdonald's paper (see page 38)

I would base the opinion that the Australian "X-disease" is a distinct entity, due to a definite specific virus, on the following points:

As detailed in the eighth report of the Microbiological Laboratory (Government Bureau of Microbiology), New South Wales, for the year 1917, one hundred and thirty-four cases came to our knowledge during the two years in which the disease chiefly manifested itself. Of these ninety-four patients died. The majority of patients showed general signs of cerebro-spinal irritation. High temperatures occurred towards the end in some fatal cases. Paralytic conditions due to involvement of the spinal cord occurred in only a few cases and never alone. The cases were not recognized as being like those of ordinary acute polio-encephalo-myelitis of the infantile paralysis type by the medical men who attended them. The latter disease was notifiable and in the districts affected during the course of the epidemics there was absolutely no increase in number of notifications of infantile paralysis. Had the virus been the same surely some cases would have conformed to the type of infantile paralysis and have been recognized as such by the medical men concerned.

The virus was conveyed obviously through Sydney and out in other directions to the dry hot western parts of the State. No cases of "X-disease," with one or two doubtful exceptions, occurred in Sydney. That the virus of ordinary infantile paralysis can flourish in Sydney is shown by the occurrence of cases. If the viruses are identical, why did not cases of ordinary infantile paralysis occur in Sydney, the virus being introduced by these carriers? It would seem as though for some reason the climatic conditions in Sydney were unfavourable to the developement of the virus of "X-disease," but we know that they are not unfavourable to the developement in the autumn of the virus of ordinary infantile paralysis.

The disease was conveyed from monkeys to a series of sheep, a calf and a foal. No one else has successfully conveyed the virus of ordinary acute polio-encephalo-myelitis to these three latter species of animals. Either the virus, therefore, was distinct from that of the latter disease or some error, such as that suggested by Flexner, crept in during the course of the inoculations or else the virus of ordinary polio-encephalo-myelitis is conveyable occasionally to these other large animals, but other observers had not carried out a sufficiently extensive series of inoculations to get positive results. I am iinclined to think that the former explanation will prove to be the correct one. At any rate I submit that the information available warrants us in retaining for the present a distinctive term for the Australian disease.

The Patho-histology of Encephalitis.

Tho patho-histological changes met with in these types of encephalitis have already been considered. How may these changes explain the clinical symptoms? The destruction of nerve cells by neurono-phagocytosis must lead to permanent failure of function. Less severe involvement may possibly enable recovery to occur. The stuffing of the perivenous sheaths with round cells must interfere with the blood supply and consequently also lead to functional disturbances. I am inclined to think that in many cases the clinical symptoms to a great extent may be attributed to the mechanical effects of these perivenous sheaths. It is probable that two independent reactions occur. One is the involvement of the noble nerve cells, the other is this lymphocytic reaction. Both may give rise to profound symptoms. One or other may be the predominant feature. It is possible that the injury to the nerve cells may really be secondary to the lymphocytic reaction. We cannot consider that the presence of the round cells in the neighbourhood of the veins indicates that the virus is located in that situation. It may be that it multiplies further out in the nerve tissues and that its toxins exert their effect in proximity to the vessel walls. The virus may perhaps flourish not only in the noble cells but in the neuroglial cells as well.

Transmission of Encephalitis.

There is nothing to suggest that any insect vector is the means of conveyance from one human being to another. There is no evidence that the human diseases are part of an epizootic affecting other animals. The ordinary way of transmission seems undoubtedly to be by means of carriers. It seems clear that during an epidemic considerable numbers of the community must be carriers and that relatively few of those who harbour from time to time the virus develope the disease. What explanation have we of this? It has been suggested that from time to time the virus is able to make progress upwards from the naso-pharynx, where it presumably first lodges, to the central nervous system. Only occasionally is an individual's resistance so lowered as to enable this to take place and hence few cases occur. Our experimental results with sheep would suggest that even when the virus does reach the brain not always does the disease develope. On several occasions we inoculated six sheep at a time with the same virus in the same way with the same amount and under the same conditions. Of such a batch of six sheep two might develope the disease and die, two might show slight symptoms and recover and two be quite unaffected. Such unaffected sheep incorporated in another batch would again give a negative result. These animals it would seem were refractory to the virus or at any rate if the virus did flourish in their brains, for some reason it failed to give rise to any reaction in the sheep as shown by lymphocytic infiltration or marked destruction of the nerve cells. If these experimental results can be relied on, it is probable that in some human beings the virus may actually reach the brain and yet not give rise to any reaction to its presence. In this connexion a consideration of febrile herpes is important. This has been shown clearly to be due to a virus capable of causing encephalitis in rabbits. Febrile herpes is of common occurrence. The virus must be widely distributed. Only occasionally does it establish itself and give rise to a reaction. If we contract an infectious cold in the head or develope lobar pneumonia or cerebro-spinal meningitis, febrile herpes may manifest itself, presumably owing to temporary lowered resistance. By similar means we can understand the viruses of encepalitis establishing themselves from time to time.

(*To be Continued.*)